

6.02 SAXAGLIPTIN 2.5mg and 5mg oral tablets, 28, Onglyza[®], AstraZeneca Australia Pty Ltd.

1 Purpose of Application

- 1.1 The submission sought to extend 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 mellitus (T2DM) in combination with metformin and a sulfonylurea (MET + SU).

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 Manufacturer	Name and
SAXAGLIPTIN				Onglyza [®]	AZ
saxagliptin 5mg tablet, 28	1	5	\$TBC		
saxagliptin 2.5mg tablet, 28	1	5	\$TBC		

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
PBS Indication:	Diabetes mellitus type 2
Restriction Level / Method:	Authority required (Streamlined)
Clinical criteria:	<p>The treatment must be in combination with metformin, AND 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 inhibitor (gliptin), a thiazolidinedione (glitazone), a glucagon-like peptide-1 or a sodium-glucose co-transporter 2 (SGLT2) 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 gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 despite treatment with maximally tolerated doses of metformin and a sulfonylurea.</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 a 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 a 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 a SGLT2 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 or a sulfonylurea does not need to requalify on this criterion before being eligible for PBS-subsidised treatment with this drug.</i></p>
Administrative Advice	<p>Note: <i>This drug is not PBS-subsidised for use as monotherapy or in combination with a thiazolidinedione (glitazone), a glucagon-like peptide-1 or an SGLT2 inhibitor.</i></p>

- 2.2 The listing was requested on a cost minimisation basis compared to insulin glargine and exenatide (including non-drug cost offsets). The submission requested that the PBAC also consider listing the saxagliptin/metformin fixed dose combination products and provided a minor submission to that effect (see agenda item 6.13).
- 2.3 The PSCR noted that if the PBAC considered that dapagliflozin was the appropriate comparator, the listing is requested on a cost minimisation basis with dapagliflozin (excluding dapagliflozin's cost offsets for urinary tract and genital infections).

For more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

- 3.1 **TGA status at time of PBAC consideration:** Saxagliptin (Onglyza®) was first listed on the Australian Register of Therapeutic Goods in March 2011, and is currently approved for use in T2DM: as an adjunct to diet and exercise in dual oral combination therapy with MET, or a SU, or a thiazolidinedione; in triple oral combination therapy with MET and a SU; and in combination with insulin. At the time of PBAC consideration, the TGA clinical evaluation and the ACPM resolution and minutes were available.
- 3.2 Saxagliptin was considered by the PBAC at the March 2010 meeting, and recommended for listing as an Authority Required (STREAMLINED) benefit for the

treatment of T2DM as dual oral therapy with MET or a SU, on the basis of a cost minimisation analysis versus sitagliptin.

- 3.3 Saxagliptin was also considered by the PBAC at the July 2012 meeting to extend the existing Authority Required (Streamlined) listing to include treatment of patients with T2DM in combination with insulin, but was rejected.
- 3.4 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 fixed dose combinations with metformin (Kombiglyze® XR, saxagliptin/metformin 2.5mg/1g, 5mg/500mg and 5mg/1g) are listed on the PBS for patients inadequately controlled on metformin alone.
- 3.5 The PBAC recommended extending the PBS listing of dapagliflozin for patients with T2DM in combination with MET + SU on a cost analysis basis compared with insulin (including drug acquisition costs and costs of healthcare resource consumption).

4 Clinical place for the proposed therapy

- 4.1 T2DM is a chronic disease characterised by hyperglycaemia and multiple long term co-morbidities. Diet control and exercise are the first steps in managing the disease, followed by the addition of MET. If blood glucose control is not achieved, treatment guidelines recommend adding a SU, another oral diabetes medicine, a glucagon like peptide 1 (GLP-1) receptor agonist or insulin. If dual therapy does not achieve control, treatment guidelines recommend adding a third diabetes medicine.
- 4.2 The submission proposed that saxagliptin be listed for triple oral therapy, in combination with MET and a SU. Other options include GLP-1 receptor agonists, other DPP-4 inhibitors ('gliptins'), thiazolidinediones ('glitazones') or acarbose.

5 Comparator

- 5.1 Insulin glargine as the main comparator and exenatide as a secondary comparator. These were appropriate comparators. However, dapagliflozin was recommended for triple oral therapy at the March 2015 meeting and may be a more appropriate main comparator. The ESC agreed that dapagliflozin is the appropriate main comparator. The Pre-PBAC Response stated that the sponsor is comfortable with dapagliflozin as the main comparator.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from a health care professional (1) via the Consumer Comments facility on the PBS website. The comment described the benefits of listing saxagliptin for triple oral therapy, including the availability of an additional treatment before considering insulin and better compliance and outcomes for patients with poorly controlled diabetes.

Clinical trials

- 6.3 The submission was based on two indirect comparisons with insulin glargine and exenatide, and a third supporting comparison with dapagliflozin:
1. Saxagliptin +MET+SU (Trial D006) vs insulin glargine +MET+SU (Russell-Jones 2009), placebo +MET+SU as common comparator;
 2. Saxagliptin +MET+SU (Trial D006) vs exenatide 5ug +MET+SU and exenatide 10ug +MET+SU (Trial 115), placebo +MET+SU as common comparator; and
 3. Saxagliptin +MET+SU (Trial D006) vs dapagliflozin +MET+SU (Matthaei 2015), placebo +MET+SU as common comparator.
- 6.4 Details of the trials presented in the submission are provided in Table 1.

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Saxagliptin vs placebo (metformin + sulfonylurea background)		
Trial D006	A 24 week, multicentre, randomised, double-blind, placebo-controlled, international phase IIIb to evaluate 5mg saxagliptin vs placebo in patients with Type 2 diabetes who have inadequate glycaemic control on a background combination of metformin and sulfonylurea. Report for the 24-week short-term treatment period. NCT01128153; D1680L00006. Moses et al. (2014) A randomized controlled trial of the efficacy and safety of saxagliptin as add-on therapy in patients with type 2 diabetes and inadequate glycaemic control on metformin plus a sulphonylurea.	18 July 2013. <i>Diabetes, Obesity and metabolism</i> 2014; 16: 443-450.
Insulin glargine vs placebo (metformin + sulfonylurea background)		
Russell-Jones 2009	A 26 week, multicentre, randomised, parallel-group, placebo controlled phase III trial to compare the efficacy and safety of liraglutide in type 2 diabetes mellitus vs placebo with an open-label treat-to-target insulin glargine control arm, all in combination with metformin and glimepiride. NCT00331851. Russell-Jones et al. (2009) Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 MET+SU): A randomised controlled trial.	15 February 2008. (Report not available) <i>Diabetologia</i> 2009; 52(10): 2046-2055.
Exenatide vs placebo (metformin + sulfonylurea background)		
Trial 115	A Phase III, randomized, double-blind, parallel-group, long-term, placebo-controlled, multicenter study to examine the effect on glucose control (HbA1c) of exenatide given twice daily in subjects with type 2 diabetes mellitus treated with metformin and a sulfonylurea. Study AC2993-115; NCT00035984. Kendall et al. (2005) Effects of exenatide (exendin-4) on glycaemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea.	27 April 2004. <i>Diabetes Care</i> 2005; 28(5): 1083-1091.
Supportive analyses		
Dapagliflozin vs placebo (metformin + sulfonylurea background)		
Matthaei 2015	A 24-week, multicentre, randomised, double-blind, placebo-controlled, international phase III Study with a 28-week extension period to evaluate the safety and efficacy of dapagliflozin 10 mg once daily in patients with Type 2 diabetes who have inadequate glycaemic control on a background combination of metformin and sulfonylurea. Report for the 24-week short-term treatment period. D1693C00005; NCT01392677. Grandy et al. (2014) Weight-related quality of life and treatment satisfaction among type 2 diabetes mellitus patients treated with dapagliflozin in triple-therapy regimen. Matthaei et al. (2014) Improvement in glycaemic control and reduction in body weight over 52 weeks with dapagliflozin as add-on therapy to metformin plus sulphonylurea. Matthaei et al. (2013) Dapagliflozin improves glycaemic control and reduces body weight as add-on therapy to metformin plus sulphonylurea.	27 September 2010. <i>Diabetes</i> 2014; 63:A204-A205. <i>Diabetologia</i> 2014; 57(1):S347. <i>Diabetologia</i> 2014; 56:S374-S375.

Source: Table B.4, p42-44 of the submission.

6.5 The key features of the randomised trials are summarised below.

Table 2: Key features of the included evidence

Trial	N	Design	Comparison	Background diabetes medicines	Patient population	Risk of bias
Saxagliptin vs placebo (metformin + sulfonylurea background)						
Trial D006 24 weeks	N=257	RCT double-blind multi centre	SAXA 5mg +MET+SU vs placebo +MET+SU	Metformin and sulfonylurea continued at pre-study doses	HbA1c 7.0%-10%	Low
Insulin glargine vs placebo (metformin + sulfonylurea background)						
Russell-Jones 2009 26 weeks	N=581	RCT open label multi centre	LIRA +MET+SU vs placebo +MET+SU vs Insulin glargine +MET+SU	Maximised metformin 2g Glimepiride 4mg	HbA1c 7.0%-10%	Low
Exenatide vs placebo (metformin + sulfonylurea background)						
Trial 115 30 weeks	N=734	RCT double-blind multi centre	EXE 5µg +MET+SU vs EXE 10µg +MET+SU vs placebo +MET+SU	Metformin ≥1500mg/day +SU at max effective dose (≥50% of max dose), or min recommended dose	HbA1c 7.5%-11%	Unclear
Dapagliflozin vs placebo (metformin + sulfonylurea background)						
Matthaei 2015 24 weeks	N=218	RCT double-blind multi centre	DAPA 10mg +MET+SU vs placebo +MET+SU	Metformin ≥1500 mg/day SU at maximum tolerated dose (≥50% of max dose)	HbA1c 7.0%-10.5%	Low

Source: compiled during the evaluation.

Abbreviations: DAPA, dapagliflozin; EXE, exenatide; HbA1c, glycated haemoglobin; LIRA, liraglutide; max, maximum; MET, metformin; min, minimum; RCT, randomised controlled trial; SAXA, saxagliptin; SU, sulfonylurea.

- 6.6 There were differences between trials in terms of baseline patient characteristics and sulfonylurea use, particularly between the saxagliptin Trial D006, and the insulin glargine trial Russell-Jones 2009 and exenatide Trial 115.
- The saxagliptin Trial D006 included a mostly Asian population (55%), but subgroup analyses showed no significant interaction between race and treatment effect (p=0.3566).
 - Baseline use of SUs varied in both the choice of SU and dose.
- 6.7 There were substantial differences between trials in terms of concomitant SU use, particularly between the saxagliptin Trial D006, and the insulin glargine trial Russell-Jones 2009 and exenatide Trial 115.
- In the saxagliptin Trial D006 patients continued on pre-trial SU regimens including several kinds of sulfonylurea. In the insulin glargine trial Russell-Jones 2009, patients were commenced on an optimised glimepiride regimen. In the exenatide Trial 115, patients were randomised (1:1), within each treatment arm, to either a minimum or maximum SU dose subgroup including several kinds of SUs.
- 6.8 It was unclear if differences in background SU regimens resulted in a bias in favour of saxagliptin or the comparators in the indirect comparisons.
- 6.9 The saxagliptin Trial D006 and the dapagliflozin trial (Matthaei 2015) were similar in design and population.

Comparative effectiveness**Table 3: Mean change in HbA1c from baseline to end point, indirect comparison between treatments**

Trial ID	Duration; population	LS mean change in HbA1c from baseline (SE)				Difference in LS mean change (95% CI)
		n	Active Treatment	n	Placebo	
Saxagliptin 5mg vs placebo (with MET + SU)						
Trial D006	24 week; FAS	127	-0.74 (0.08)	127	-0.08 (0.07)	-0.66 (-0.86, -0.47)
Insulin glargine (mean dose 24IU) vs placebo (with MET + SU)						
Russell-Jones 2009	26 week; ITT	232	-1.09 (0.09)	114	-0.24 (0.11)	-0.85 (-1.04, -0.66)
Exenatide 10µg BID vs placebo (with MET + SU)						
Trial 115	30 week; ITT	241	-0.88 (0.08)	247	0.12 (0.08)	-1.00 (-1.20, -0.80)
	24 week; ITT		-1.04 (0.08)		0.06 (0.08)	-1.10 (-1.29, -0.92)
	30 week; Max SU	119	-1.05 (0.12)	120	-0.03 (0.11)	-1.02 (-1.30, -0.73)
Exenatide 5µg BID vs placebo (with MET + SU)						
Trial 115	30 week; ITT	245	-0.66 (0.08)	247	0.12 (0.08)	-0.78 (-0.98, -0.58)
	24 week; ITT		-0.72 (0.07)		0.06 (0.08)	-0.78 (-0.97, -0.60)
	30 week; Max SU	123	-0.80 (0.11)	120	-0.03 (0.11)	-0.77 (-1.05, -0.49)
Dapagliflozin 10mg vs placebo (with MET + SU)						
Matthaei 2015	24 week; FAS	108	-0.86 (0.07)	108	-0.17 (0.07)	-0.69 (-0.89, -0.49)
Indirect comparisons						
Saxagliptin vs insulin glargine (with MET + SU)					24/26 weeks	0.19 (-0.08, 0.46)
					24/30 weeks	0.34 (0.06, 0.62)
Saxagliptin vs exenatide 10µg BID (with MET + SU)					24/24 weeks	0.44 (0.17, 0.71)
					24/30 Max SU weeks	0.36 (0.02, 0.71)
Saxagliptin vs exenatide 5µg BID (with MET + SU)					24/30 weeks	0.12 (-0.16, 0.40)
					24/24 weeks	0.12 (-0.24, 0.48)
					24/30 Max SU weeks	0.11 (-0.23, 0.45)
Saxagliptin vs dapagliflozin (with MET + SU)					24/24 weeks	0.03 (-0.25, 0.31)

Source: Table B-48, p.112 of the submission; Table B.23, p.31 of the Section B Dapagliflozin Supplementary Evaluation.

Abbreviations: CI, confidence interval; FAS, full analysis set; HbA1c, Glycosylated haemoglobin; ITT, intention to treat; LS, least squares; Max SU, maximum sulfonylurea dosing; MET, metformin; PP, per protocol; SE, standard error; SU, sulfonylurea.

Note: Negative differences favour active treatment. In the indirect comparisons, negative differences favour saxagliptin. Statistically significant results in bold.

- 6.10 The addition of saxagliptin 5mg, dapagliflozin 10mg, insulin glargine (titrated to effect) or exenatide 5 or 10µg twice daily to background MET and a SU produced statistically significant reductions in HbA1c compared to placebo over 24 to 30 weeks.
- 6.11 Based on the indirect comparisons:
- saxagliptin 5mg showed no statistically significant difference compared to insulin glargine or exenatide 5µg twice daily, but did not demonstrate non-inferiority to insulin glargine or exenatide, with the upper limit of the confidence intervals exceeding the MCID of 0.4%;
 - exenatide 10µg twice daily showed clinically meaningful and statistically significantly larger reductions in HbA1c compared to saxagliptin 5mg; and
 - saxagliptin 5mg demonstrated non-inferiority to dapagliflozin 10mg, with an upper limit of the confidence interval of 0.31%.
- 6.12 Saxagliptin, insulin glargine, exenatide and dapagliflozin reported statistically significantly higher proportions of patients achieving HbA1c <7% versus placebo. In

the indirect comparisons there were no statistically significant differences between saxagliptin and the comparators.

- 6.13 Patients taking saxagliptin and insulin glargine reported statistically significant weight gain compared with placebo, while patients taking exenatide and dapagliflozin reported statistically significantly more weight loss compared to placebo. In the indirect comparisons, saxagliptin resulted in statistically significantly less weight gain compared to insulin glargine but significantly more weight gain compared to dapagliflozin.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Comparative harms

- 6.14 There were no statistically significant differences between saxagliptin and dapagliflozin or between saxagliptin and insulin glargine in terms of the proportion of patients reporting adverse events, including hypoglycaemia.
- 6.15 There were no statistically significant differences in serious adverse events or hypoglycaemia between saxagliptin and exenatide 5µg. However, a statistically significantly lower proportion of saxagliptin patients reported at least one adverse event compared to both exenatide 5µg and 10µg, and there were statistically significantly more hypoglycaemia events and discontinuations in patients treated with exenatide 10µg.
- 6.16 The safety profiles of saxagliptin and dapagliflozin were similar, but dapagliflozin is associated with genital and urinary tract infections.
- 6.17 Results of the recently reported Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus study (SAVOR; N=16,492), suggested a 27% increase in the rate of hospitalisations for heart failure in patients treated with saxagliptin compared to placebo (HR 1.27, 95% CI [1.07, 1.51]). However, a subsequent FDA review of these data (14 April 2015) found the cardiovascular risk of saxagliptin was acceptable. There are no current TGA safety alerts for saxagliptin. The PSCR provided a summary of the results from the SAVOR study. It acknowledged the increased rate of hospitalisation for heart failure in patients treated with saxagliptin and noted that this information has been incorporated into the Company Core Risk Management Plan and the Australian Product Information (TGA approved 21 April 2015). It also stated that SAVOR met the primary safety endpoint – demonstrating that saxagliptin did not increase the composite risk for cardiovascular death, nonfatal myocardial infarction and nonfatal ischemic stroke when added to a patient's current standard of care (with or without other antidiabetic therapies), as compared to placebo and argued that "the entire body of evidence should be considered when determining whether the PBS use of saxagliptin should be broadened, not just one component of the secondary outcome."
- 6.18 On 15 May 2015, the FDA issued a warning that use of SGLT2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids called ketones, which may require hospitalization. The European Medicines Agency's Pharmacovigilance

Risk Assessment Committee has recently commenced a review of SGLT2 inhibitors to evaluate the risk of diabetic ketoacidosis.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Clinical claim

- 6.19 The submission described saxagliptin 5mg as similar in terms of comparative effectiveness and non-inferior in terms of comparative safety to insulin glargine 24IU/day (in combination with MET and a SU):
- This claim may not be adequately supported in terms of comparative efficacy. The indirect comparison showed no statistically significant difference in reduction of HbA1c between saxagliptin 5mg and insulin glargine 24IU daily. However, the upper limit of the 95% confidence interval exceeded the accepted MCID of 0.4% and non-inferiority was not demonstrated.
 - In terms of safety, saxagliptin was associated with less weight gain compared with insulin glargine, and a lower risk of hypoglycaemia events in the long term safety studies.
- 6.20 The submission described saxagliptin 5mg as similar in terms of comparative effectiveness and non-inferior in terms of comparative safety to exenatide 5µg and 10µg twice daily (in combination with MET and a SU):
- This claim was not adequately supported in terms of comparative efficacy. The indirect comparison showed no statistically significant difference in reduction of HbA1c between saxagliptin 5mg daily and exenatide 5µg twice daily. However, the upper limit of the 95% confidence interval exceeded the accepted MCID of 0.4%, and therefore did not demonstrate non-inferiority.
 - Exenatide 10µg twice daily showed clinically meaningful and statistically significantly larger reductions in HbA1c compared to saxagliptin 5mg, and may be superior.
- 6.21 The submission described saxagliptin 5mg as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety to dapagliflozin 10mg daily (in combination with MET and a SU):
- This claim was adequately supported in terms of comparative efficacy. The indirect comparison showed no statistically significant difference in reduction of HbA1c between saxagliptin 5mg and dapagliflozin 10mg. The upper limit of the 95% confidence interval was within the accepted MCID of 0.4% (0.31%), demonstrating non-inferiority.
 - This claim may be adequately supported in terms of safety. The safety profile of saxagliptin is different to that of dapagliflozin, with dapagliflozin being associated with an increased incidence of genitourinary tract infections requiring treatment, particularly in women.
- 6.22 The ESC considered that dapagliflozin was the appropriate main comparator and that the claim of non-inferiority in terms of comparative effectiveness was adequately supported. The ESC noted the differences in the safety profiles of saxagliptin and dapagliflozin but considered that the claim of non-inferior comparative safety was adequately supported.

- 6.23 The PBAC considered that the claim of non-inferior comparative effectiveness to dapagliflozin was reasonable.
- 6.24 The PBAC noted that saxagliptin has a different safety profile to dapagliflozin but considered that the claim of non-inferior comparative safety was reasonable.
- 6.25 The PBAC considered that the claim of similar effectiveness and non-inferior comparative safety to insulin glargine may not have been adequately supported by the data.
- 6.26 The PBAC did not accept the claim of similar effectiveness and non-inferior comparative safety to exenatide.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Economic analysis

- 6.27 The submission presented a cost minimisation analysis versus insulin glargine and exenatide, with a cost analysis including non-drug costs related to administration and diabetes management. An analysis versus dapagliflozin was not presented in the submission.
- 6.28 The equi-effective doses were estimated as saxagliptin 5mg (oral) = insulin glargine 24 IU/day (subcutaneous) = exenatide 20µg (subcutaneous). The equi-effective doses were derived from indirect comparisons using trials that may not be exchangeable and that did not demonstrate non-inferiority between saxagliptin and the comparators.

Table 4: Cost analysis: derived price for saxagliptin based on avoided costs associated with treatment with insulin glargine and exenatide

Description	Saxagliptin	Insulin glargine	Exenatide
Assumed effective ex-manufacturer price	-	\$ [REDACTED]	5µg: \$53.76 10µg: \$76.80
Treatment initiation (pro-rated over 3 years)			
GP consultations	\$ [REDACTED] ([REDACTED])	\$12.35 (1/year)	\$12.35 (1/year)
Endocrinologist consultations	0	\$28.52 (1/year)	0
Diabetes educator visits	0	\$28.78 (1/year)	\$28.78 (1/year)
Treatment titration to stabilisation (pro-rated over 3 years)			
GP consultations	\$ [REDACTED] ([REDACTED])	\$49.40 (4/year)	\$12.35 (1/year)
Diabetes educator visits	0	\$21.10 (1/year)	0
Ongoing management (per year)			
Blood glucose monitoring (glucose indicator test strip)	\$ [REDACTED] ([REDACTED])	\$533.27 (2/day)	\$266.63 (1/day)
Needles for insulin pen	0	\$47.48 (1/day)	\$94.97 (2/day)
Community nurse visits	-	\$5.32 (0.07/year)	-
Derived price for saxagliptin, 5mg, 28			
Total non-drug cost of treatment	\$ [REDACTED]	\$726.22	\$415.08
Incremental non-drug cost of treatment	-	\$434.89	\$123.75
Incremental non-drug cost (28 days)	-	\$33.34	\$9.49
Total incremental cost of drug and non-drug treatment (28 days)	-	\$ [REDACTED]	5µg: \$75.59 10µg: \$101.02
Weighted price (and weightings) for saxagliptin (DPMQ)	\$ [REDACTED]	(75.8%)	(5µg: 5.9%) (10µg: 18.3%)

Source: Compiled during the evaluation.

- 6.29 If insulin glargine and exenatide were the appropriate comparators, the ESC considered it would be more appropriate to conduct the cost analysis against insulin glargine only, since non-inferiority to exenatide had not been adequately demonstrated. In this case, the ESC noted that the cost offsets accepted by the PBAC for dapagliflozin triple oral therapy versus insulin glargine should apply to saxagliptin (with the possible exception of the cost for urinary tract and genital infections). The PSCR noted that conducting the cost minimisation against insulin glargine alone would be consistent with the approach taken for dapagliflozin in triple oral therapy and that the expected price of saxagliptin using this approach would be identical to that of dapagliflozin, excluding offsets for genital and urinary tract infections.
- 6.30 However, the ESC considered that dapagliflozin was the appropriate comparator and therefore a cost minimisation analysis versus dapagliflozin (recommended for triple oral therapy at the March 2015 meeting) would be more appropriate. The PSCR noted that the sponsor was willing to accept the current dapagliflozin price for saxagliptin, excluding offsets for urinary tract and genital infections.
- 6.31 The PSCR noted that the therapeutic relativity sheets (as at 1 June 2015) state:
- dapagliflozin 10 mg as equi-effective dose to sitagliptin 100 mg, and
 - sitagliptin 100 mg as equi-effective dose to saxagliptin 5 mg.
- By inference, the PSCR claimed that dapagliflozin 10 mg is equi-effective to saxagliptin 5 mg.

- 6.32 The submission noted that saxagliptin is currently listed for dual oral therapy in combination with metformin or a sulfonylurea (\$59.20, DPMQ), and requested a weighted price across listings. The PSCR claimed that whether insulin glargine or dapagliflozin is the main comparator, it expects that the final price for saxagliptin will be unchanged from the current PBS price (i.e. \$44.34 per pack ex-manufacturer or \$59.20 DPMQ).

For more detail on PBAC’s view, see section 7 “PBAC outcome”

Drug cost/patient/year: \$ [REDACTED]

- 6.33 At the DPMQ requested in the submission of \$ [REDACTED] for a 28 tablet pack of saxagliptin, the drug cost per patient per year would have been \$ [REDACTED] (assuming 13.04 packs per year). At a DPMQ of \$ [REDACTED], the drug cost per patient per year for saxagliptin would be \$ [REDACTED].

Estimated PBS usage & financial implications

- 6.34 This submission was not considered by DUSC. The submission presented a market share approach, with estimates based on extrapolated trends of use in triple therapy derived from an analysis of the 10% Medicare sample. The submission did not expect that listing of saxagliptin for triple oral therapy would increase the overall market size, but acknowledged that the reimbursed market may increase in size as patients using diabetes medicines outside PBS listed restrictions switch to saxagliptin.
- 6.35 The submission included substantial non-drug related costs derived from differences in the costs of administration and diabetes management between saxagliptin and the comparators.

Table 5: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Market share	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %
Scripts ^a	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated net cost to PBS/RPBS					
Cost of drug to PBS/RPBS	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Savings from substituted drugs	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Net cost to PBS/RPBS	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Estimated net cost to MBS					
Net savings to MBS	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]

Source: Compiled during the evaluation.

^a Assuming 13.04 per year as estimated by the submission.

- 6.36 The redacted table above shows that at year 5, the estimated number of patients was less than 10,000 and the number of scripts was between 100,000 and 200,000; and the net cost to the PBS/RPBS would be less than \$10 million.
- 6.37 The submission estimated that extending the listing of saxagliptin to include triple therapy will result in a small additional cost to the PBS, and savings to government

health budgets of similar magnitude, resulting in a small overall savings to government. The estimated net savings are most likely an overestimate:

- estimated non-drug related savings derived from reductions in GP, endocrinologist, diabetes educator and community nurse visits and blood glucose monitoring were not adequately justified, and unlikely to be realised in clinical practice;
- the price of saxagliptin used in the estimates was derived from a cost minimisation versus insulin glargine and exenatide, where non-inferiority was not demonstrated;
- estimated base case utilisation assumed the triple therapy market comprised insulin glargine and exenatide only, and therefore overestimated the savings likely to be derived from saxagliptin substituting other less costly oral diabetes medicines;
- the use of the cost of insulin glargine as a proxy for all basal and pre-mixed insulins likely to be substituted by saxagliptin, overestimated savings likely to be derived from saxagliptin substituting other less costly basal and pre-mixed insulins.

- 6.38 The PSCR noted that the objective of the price proposed for this listing (i.e. the current PBS price for saxagliptin) is that the listing should be cost-neutral to Government health budgets.

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of saxagliptin for the treatment of T2DM in combination with MET and SU (triple oral therapy). The recommendation was formed on the basis of a cost-minimisation analysis compared with dapagliflozin in combination with MET and a SU. The equi-effective doses are saxagliptin 5mg and dapagliflozin 10mg.
- 7.2 The PBAC accepted that saxagliptin used in combination with MET and a SU is non-inferior to dapagliflozin in combination with MET and a SU in terms of clinical effectiveness and safety.
- 7.3 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).
- 7.4 The PBAC recommended that the listing for saxagliptin should be consistent with the triple oral therapy restriction for sitagliptin. The PBAC further recommended that this restriction wording should apply to other DPP-4 inhibitors and SGLT2 inhibitors 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).

- 7.5 The PBAC considered there was a clinical place for saxagliptin in triple oral therapy, noting that it may delay the introduction of insulin. As an aside, the PBAC noted that it did not see a clinical need for any future submissions requested listing for saxagliptin in combination with metformin, a sulfonylurea and insulin (triple oral therapy and insulin).
- 7.6 The PBAC recalled that dapagliflozin was recommended for listing for triple oral therapy in March 2015. Dapagliflozin was recommended on the basis of a cost analysis compared with insulin (including drug acquisition costs and costs of healthcare resource consumption). The PBAC agreed with ESC that dapagliflozin was the appropriate main comparator.
- 7.7 The PBAC considered that saxagliptin has a different, but not worse, safety profile than dapagliflozin as measured by the occurrence of adverse events, significant adverse events and discontinuations due to adverse events.
- 7.8 The PBAC noted that the PSCR claimed that the objective of the price proposed for this listing is that the listing should be cost-neutral to Government health budgets.
- 7.9 The PBAC advised the Minister that, under Section 101(3BA) of the National Health Act 1953, saxagliptin should be treated as interchangeable on an individual patient basis with sitagliptin for triple oral therapy for T2DM.
- 7.10 The PBAC advised that the NOTE in the current restriction of saxagliptin dual therapy will need to be amended to allow for triple oral combination therapy.
- 7.11 The PBAC advised that saxagliptin is suitable for prescribing by nurse practitioners within collaborative arrangements.
- 7.12 The PBAC recommended that the Safety Net 20 Day Rule should apply.

Outcome:

Recommended

8 Recommended listing

- 8.1 Amend existing listing as follows:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
SAXAGLIPTIN			Onglyza®	AZ
saxagliptin 5mg tablet, 28	1	5		
saxagliptin 2.5mg tablet, 28	1	5		
Category / Program	GENERAL – General Schedule (Code GE)			
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners			
PBS Indication:	Diabetes mellitus type 2			

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Restriction Method:	Level /	Authority required (Streamlined)
Clinical criteria:		<p>The treatment must be in combination with metformin, AND 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 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; 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 gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 despite treatment with either metformin and a sulfonylurea, or metformin and this drug, or a sulfonylurea and this drug.</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 a 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 a SGLT2 inhibitor was initiated.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances: a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or 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 a 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 or a sulfonylurea does not need to requalify on this criterion before being eligible for PBS-subsidised treatment with this drug.</p>
Administrative Advice		<p>Note: This drug is not PBS-subsidised for use as monotherapy or in combination with a thiazolidinedione (glitazone), a glucagon-like peptide-1 or an SGLT2 inhibitor.</p>

9 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.

10 Sponsor's Comment

The sponsor had no comment