

**6.04 SITAGLIPTIN 25mg, 50mg, 100mg tablet;
SITAGLIPTIN + METFORMIN 50/500mg, 50/850mg, 50/1000mg tablet;
SITAGLIPTIN + METFORMIN XR, 50/1000mg, 100/1000mg tablet;
Januvia®, Janumet®, Janumet XR®
Merck Sharp & Dohme Australia Pty Ltd.**

1 Purpose of Application

1.1 The submission sought to extend the PBS listing of sitagliptin, sitagliptin+metformin and sitagliptin+metformin XR to include an Authority Required (Streamlined) listing for the treatment of patients with type 2 diabetes mellitus (T2DM) in combination with insulin, with or without metformin.

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary and Manufacturer	Name
SITAGLIPTIN sitagliptin 25 mg tablet, 28 sitagliptin 50 mg tablet, 28 sitagliptin 100 mg tablet, 28	1	5	Januvia®	MK
SITAGLIPTIN + METFORMIN sitagliptin 50 mg + metformin hydrochloride 500 mg tablet, 56 sitagliptin 50 mg + metformin hydrochloride 850 mg tablet, 56 sitagliptin 50 mg + metformin hydrochloride 1 g tablet, 56	1	5	Janumet®	MK
SITAGLIPTIN + METFORMIN sitagliptin 50 mg + metformin hydrochloride 1 g tablet: modified release, 56 sitagliptin 100 mg + metformin hydrochloride 1 g tablet: modified release, 28	1	5	Janumet XR®	MK

Category / Program	GENERAL – General Schedule (GE)
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Restriction Level / Method:	Authority required (Streamlined)

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Clinical criteria:	<p>The treatment must be in combination insulin</p> <p>AND</p> <p>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 insulin with or without other oral antidiabetic agents <i>insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated;</i></p> <p>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 prior to initiation with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor despite treatment with insulin with or without other oral antidiabetic agents <i>insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated;</i></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>
Administrative Advice	<p>Note</p> <p><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 Pre-Sub-Committee Response (PSCR) disagreed with the change in restriction wording suggested by the secretariat, stating that the additional wording “insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated” was unnecessary as the requested restriction was “similar to the recommendation and acceptable”. However, the ESC agreed with the secretariat that the restriction wording should be changed, citing consistency with the dapagliflozin (with insulin) listing and quality use of medicines.

2.3 The listing was requested on a cost minimisation basis compared to dapagliflozin and dapagliflozin + metformin concomitant regimens, assuming cost-offsets applied in the PBS dual therapy listing will apply to the listing of dapagliflozin and sitagliptin when used in combination with insulin.

3 Background

- 3.1 **TGA status at time of PBAC consideration:** Sitagliptin (Januvia[®]) was first listed on the Australian Register of Therapeutic Goods in January 2008, and is currently approved for use in T2DM: as an adjunct to diet and exercise in monotherapy and dual oral combination therapy with metformin, or a sulfonylurea, or a thiazolidinedione; in triple oral combination therapy with metformin and a sulfonylurea; and in combination with insulin.
- 3.2 Sitagliptin+metformin fixed dose combinations (Janumet[®], Janumet XR[®]) are currently approved for use as initial or continuing dual oral therapy in combination with metformin or a sulfonylurea, as triple combination therapy with MET and a SU when combination therapy with both agents does not provide adequate glycaemic control, and in combination with insulin.
- 3.3 Sitagliptin (March 2008 meeting) is listed on the PBS for dual oral therapy with metformin or a sulfonylurea. Sitagliptin+metformin fixed dose combinations (Janumet[®], March 2009 meeting; Janumet XR[®], November 2013 meeting) are listed on the PBS for T2DM (excluding triple oral therapy, and initial therapy). Sitagliptin was recommended for listing for triple oral therapy at the July 2015 meeting. Sitagliptin has not previously been considered by the PBAC for the treatment of T2DM in combination with insulin.

4 Clinical place for the proposed therapy

- 4.1 T2DM in combination with insulin, with or without metformin when therapy with insulin (\pm metformin) does not provide adequate glycaemic control.
- 4.2 Alternative agents used in combination with insulin include diabetes medicines, both listed and not listed on the PBS:
- up titration of basal insulins;
 - pre-mixed and rapid acting insulins;
 - other oral diabetes medicines; i.e. sulfonylureas, other DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, pioglitazone and acarbose; and
 - fixed dose combinations of oral diabetes medicines with metformin (where available).

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

5 Comparator

- 5.1 Dapagliflozin. This was the appropriate comparator. Exenatide and basal insulin were appropriate secondary comparators but were not considered in the submission.

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 that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on two indirect comparisons between sitagliptin 100mg and dapagliflozin 10mg, with placebo + insulin (\pm metformin) as common comparator:

- Sitagliptin + insulin \pm metformin versus placebo + insulin \pm metformin (Trial P051 and Trial P260).
- Dapagliflozin + insulin \pm metformin versus placebo + insulin \pm metformin (Wilding et al. 2012).

6.4 Meta-analysis of the two sitagliptin trials prior to undertaking the indirect comparison was not attempted due to differences in trial design. This was appropriate.

6.5 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/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
P051	Clinical Study Report Protocol 051. Phase III, multicenter, randomized, double-blind clinical trial to study the safety and efficacy of the addition of sitagliptin (mk-0431) to patients with type 2 diabetes mellitus who have inadequate glycemic control on insulin therapy (alone or in combination with metformin) Viisboll T, Rosenstock J, H. Yki-Jarvinen, W. T. Cefalu, Y. Chen, E. Luo, B. Musser, P. J. Andryuk, Y. Ling, K. D. Kaufman, J. M. Amatruda, S. S. Engel & L. Katz. Efficacy and safety of sitagliptin when added to insulin therapy in patients with type 2 diabetes.	January 2009. <i>Diabetes, Obesity and Metabolism</i> , 2012, 12: 167–177.
P260	Clinical Study Report Protocol 260. Phase III, multicenter, randomized, double-blind, placebo-controlled clinical trial to study the safety and insulin-sparing efficacy of the addition of sitagliptin in patients with type 2 diabetes mellitus who have inadequate glycaemic control on insulin alone or in combination with metformin	November 2013.
Wilding et al. 2012	Wilding JP, Woo V, Soler NG, Pahor A, Sugg J, Rohwedder K, Parikh S; Dapagliflozin 006 Study Group. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial.	<i>Annals of Internal Medicine</i> , 2012, Mar 20; 156(6):405-15.

Source: Table B.2-2 page 60 of the submission.

6.6 The key features of the randomised trials are summarised in Table 2.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Comparison/ outcomes	Background diabetes medicines	Patient population
Sitagliptin vs placebo						
P051	Total N=641* Placebo N=319 SITA 100mg N=322	Randomised double-blind 24 weeks	Low	SITA + INS ± MET vs Pbo + INS ± MET HbA1c, FPG, PPG, weight, HbA1c <7%.	On insulin alone or insulin + metformin (at least 1500mg/day). Included insulin therapies were pre-mixed; intermediate or long- acting.	Aged ≥21 years with T2D. HbA1c ≥7.5% and ≤11%. BMI >20 and <43 kg/m ² .
P260	Total N=660* Placebo N=330 SITA 100mg N=330	Randomised double-blind 24 weeks	Low	SITA + INS ± MET vs Pbo + INS ± MET Mean daily insulin dose, HbA1c, FPG, PPG, weight.	On insulin alone or insulin + metformin (at least 1500mg/day). Included insulin therapies were pre-mixed; intermediate or long- acting ≥15IU/day.	Aged ≥18 and ≤80 years with T2D. HbA1c ≥7.5% and ≤11%. BMI >20 and <43 kg/m ² .
Dapagliflozin vs placebo						
Wilding 2012	Total N= 808* Placebo N=197 DAPA 2.5mg N=202 DAPA 5mg N=212 DAPA 10mg N=196	Randomised double-blind 24 weeks	Low	DAPA + INS ± MET vs Pbo + INS ± MET HbA1c, FPG, weight, mean daily insulin dose.	Stable insulin regimen with mean daily dose of insulin of 30IU or more for at least 8 weeks before randomization and at least 1500mg/day or maximum tolerated dose of metformin.	Aged ≥18 and ≤80 years with T2D. HbA1c ≥7% and ≤10.5%. BMI ≤45 kg/m ² .

Source: Table B.4-3, p.81 of the submission.

Abbreviations: BMI, body mass index; DAPA, dapagliflozin; FPG fasting plasma glucose; HbA1c, glycosylated haemoglobin; INS, insulin; MET, metformin; Pbo, placebo; PPG, post-prandial glucose; SITA, sitagliptin; T2D, type 2 diabetes.

* Randomised.

6.7 The baseline characteristics of the trial populations were broadly similar and were likely to match the proposed PBS population. However, all trials excluded patients reporting a significant history of cardiovascular, renal or hepatic disease while the PBS population will include patients with these conditions.

6.8 There were substantial differences in baseline mean daily insulin doses and insulin dose management between trials. The ESC considered that Trial P260 and Wilding 2012 were not comparable in terms of reduction in mean daily insulin dose. The baseline characteristics of the trial populations are presented in Table 3.

Table 3: Baseline characteristics of the participants in the direct randomised trials varying across randomised groups

Trial	P051		P260		Wilding 2012	
	Sitagliptin	Placebo	Sitagliptin	Placebo	Dapagliflozin	PBO
N	322	319	329	329	194	193
Demographic characteristics						
Age: mean years (SD)	58.3 (9.1)	57.2 (9.3)	59.3 (8.9)	58.3 (9.7)	59.3 (8.8)	58.8 (8.6)
Male: %	157 (49)	169 (53)	151 (45.9)	164 (49.8)	87 (44.8)	95 (49.2)
Caucasian: n %	228 (71)	219 (69)	238 (72.3)	220 (66.9)	184 (94.8)	186 (96.4)
Black: n %	21 (6)	23 (7)	18 (5.5)	9 (2.7)	5 (2.6)	6 (3.1)
Asian: n %	55 (17)	61 (19)	32 (9.7)	34 (10.3)	3 (1.5)	0
Other: n %	18 (6)	16 (5)	41 (12.4)	66 (20.0)	2 (1.0)	1 (0.5)
Weight: mean kg (SD)	86.5 (18.6)	87.3 (17.9)	87.1 (19.5)	88.3 (22.6)	94.5 (19.8)	94.5 (16.8)
BMI: mean kg/m ² (SD)	31 (5)	31 (5)	31.9 (5.8)	32.2 (6.6)	33.4 (5.1)	33.1 (5.9)
Background oral anti-diabetes drugs						
None	93 (28.9)	86 (27.0)	NR	NR	96 (49.5)	96 (49.7)
Metformin alone	229 (71)	233 (73)	NR	NR	83 (42.8)	78 (40.4)
Met + SU	NR	NR	NR	NR	8 (4.1)	13 (6.7)
Diabetes specific characteristics						
HbA1c: % mean (SD)	8.7 (0.9)	8.6 (0.9)	8.66 (0.98)	8.81 (1.03)	8.57 (0.82)	8.47 (0.77)
FPG (mmol/L) mean (SD)	175.6 (51.8)	178.7 (59.6)	176.1 (46.5)	176.8 (45.9)	173.1 (54.9)	170.6 (57.2)
Duration of illness, years (SD)	13 (7)	12 (6)	13.2 (6.0)	13.7 (6.4)	14.2 (7.3)	13.5 (7.3)
Mean daily insulin dose, IU (SD)	Mix: 67.4 (35.4) LA: 44.2 (29.9)	Mix: 74.5 (36.9) LA: 44.5 (25.7)	37.3 (20.8)	36.6 (21.3)	78.0 (45.0)	73.7 (42.4)

Source: Table B.4-4, p.84 of the submission.

Abbreviations: BMI, body mass index; HbA1c; glycated haemoglobin; FPG, fasting plasma glucose; LA long-acting insulin; MET metformin; Mix, pre-mixed insulin; NR, not reported; SD, standard deviation; SU sulfonylurea.

- 6.9 The trial designs and objectives varied substantially between trials. Trial P051 and Wilding 2012 assessed glycaemic control (i.e. change from baseline in HbA1c) as the primary outcome. The primary objective of Trial P260 was to assess the insulin-sparing effect of adding sitagliptin therapy to a regimen of insulin with or without metformin, and patients were instructed to titrate doses of insulin glargine to achieve the treatment target of fasting glucose 72-100mg/dL (4.0-5.6mmol/L). Accordingly, the ESC considered that the insulin sparing effects of these regimes could not be compared. The PSCR acknowledged the differences between Trial P260 (sitagliptin) and Wilding 2012 (dapagliflozin), but reiterated that patients treated with sitagliptin and dapagliflozin demonstrated smaller changes in daily insulin dose over the course of the trials compared to placebo (-4.7 vs. -6.82 IU/day). Furthermore, the PSCR argued that as trial P260 was designed as an insulin sparing trial, the data provided robust estimates of the insulin sparing effect of sitagliptin. The ESC noted that this was reasonable for the comparison against placebo but was not comparable to dapagliflozin.
- 6.10 The pre-PBAC response stated that “it could reasonably be inferred that sitagliptin would result in insulin up-titration avoided of between 26.5IU and 28.2IU (as established in the dapagliflozin insulin submission reviewed by PBAC November 2014 – dapagliflozin PSD paragraph 7.5)”. The response based this argument on the therapeutic relativity between sitagliptin and dapagliflozin accepted by the PBAC for dual oral therapy in terms of reduction in HbA1c.

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

Comparative effectiveness

Table 4: Mean change in HbA1c from baseline to end point, indirect comparison between treatments

Treatment group	Baseline HbA1c Mean (SD)	Week 24 HbA1c Mean (SD)	LS mean change from baseline HbA1c (95% CI)	Difference in LS mean change in HbA1c (95% CI)
P051 (primary outcome)				
Sitagliptin 100mg (n=305)	8.72 (0.88)	8.07 (1.04)	-0.59 (-0.7, -0.48)	-0.56 (-0.7, -0.42)
Placebo (n=312)	8.64 (0.95)	8.58 (1.17)	-0.03 (-0.14, 0.08)	
P260 (secondary outcome)				
Sitagliptin 100mg (n=329)	8.66 (0.98)	7.34 (1.08)	-1.31 (-1.43, -1.20)	-0.45 (-0.60, -0.29)
Placebo (n=329)	8.81 (1.03)	7.90 (1.21)	-0.87 (-0.98, -0.75)	
Wilding 2012 (primary outcome)				
Dapagliflozin 10mg (n=173)	8.57 (0.82)	NR	-0.96 (NR)	-0.57 (-0.72, -0.42)
Placebo (n=166)	8.47 (0.77)	NR	-0.39 (NR)	
Indirect comparisons				
Sitagliptin 100mg (P051) versus dapagliflozin 10mg (Wilding 2012)				0.01 (-0.195; 0.215)
Sitagliptin 100mg (P260) versus dapagliflozin 10mg (Wilding 2012)				0.12 (-0.096; 0.336)

Source: Tables B.6-1, p.88, Table B.6-5, p.95, Table B.6-8 p.97 and Table B.6-9, p.100 of the submission.

Abbreviations: SD standard deviation; LS least squares; CI confidence interval; NR not reported.

Note: Statistically significant results in bold.

- 6.11 The addition of sitagliptin 100mg or dapagliflozin 10mg to background insulin regimens (\pm metformin) produced statistically significant reductions in HbA1c compared to placebo over 24 weeks.
- 6.12 Based on the indirect comparisons, sitagliptin 100mg showed no statistically significant difference compared with dapagliflozin 10mg, and demonstrated non-inferiority with the upper limit of the confidence intervals falling below the MCID of 0.4% in both comparisons.
- 6.13 Patients taking sitagliptin 100mg and dapagliflozin 10mg reported statistically significant reductions in fasting plasma glucose and 2-hour post-prandial glucose compared to placebo.
- 6.14 Patients taking sitagliptin 100mg reported no statistically significant differences in change in body weight compared with placebo. However, patients taking dapagliflozin 10mg reported statistically significant weight loss compared with placebo (between group difference -2.04kg (95% CI: -2.59, 1.48)).
- 6.15 No evidence was presented supporting the comparative efficacy of sitagliptin 25mg and 50mg strengths or sitagliptin+metformin fixed dose combinations (immediate and extended release). The submission requested the PBAC recommend these products on the basis of previous decisions accepting the clinical need for the lower dose strengths and place in therapy of the fixed dose combinations.

Comparative harms

6.16 A summary of key adverse events reported in the trials is provided in the table below.

Table 5: Summary of adverse events

Number (%) of patients	P051		P260		Wilding 2012		
	Sitagliptin	Placebo	Sitagliptin	Placebo	Dapagliflozin		Placebo
					10mg	pooled*	
N	322	319	329	329	196	610	197
With ≥1 AEs	168 (52.2)	137 (42.9)	213 (64.7)	230 (69.9)	145 (74.0)	451 (74.0)	144 (73.1)
Drug-related AEs	50 (15.52)	27 (8.5)	48 (14.6)	73 (22.2)	57 (29.1)	162 (26.6)	41 (20.8)
Serious AEs	20 (6.2)	11 (3.4)	13 (4.0)	12 (3.6)	23 (11.7)	69 (11.3)	26 (13.2)
Deaths	0	0	2 (0.6)	1 (0.3)	0	0	0
Discontinued AEs	11 (3.4)	4 (1.3)	6 (1.8)	6 (1.8)	10 (5.1)	32 (5.2)	9 (4.6)
Drug-related discontinuations	3 (0.9)	0	4 (1.2)	2 (0.6)	1 (0.5)	3 (0.5)	0
Discontinued SAEs	5 (1.6)	2 (0.6)	0	2 (0.6)	5 (2.6)	12 (2.0)	3 (1.5)
Hypoglycaemia							
≥1 event	50 (15.5)	25 (7.8)	93 (28.3)	144 (43.8)	105 (53.6)	345 (56.6)	102 (51.8)
with assistance	0	0	6 (1.8)	9 (2.7)	NR	NR	NR
with medical assist.	2 (0.6)	1 (0.3)	4 (1.2)	4 (1.2)	3 (1.5)	8 (1.3)	2 (1.0)
Genital infections All					21 (10.7)	55 (9.0)	5 (2.5)
Men	NR	NR	NR	NR	8 (9.1)	NR	0
Women					13 (12.0)	NR	5 (5.1)
Urinary tract infection	9 (2.8)	6 (1.9)	14 (4.3)	17 (5.2)	20 (10.2)	59 (9.7)	10 (5.1)
URTI	10 (3.1)	11 (3.4)	15 (4.6)	6 (1.8)	9 (4.6)	23 (3.8)	12 (6.1)
Nasopharyngitis	10 (3.1)	8 (2.5)	13 (4.0)	26 (7.9)	25 (12.8)	92 (15.1)	23 (11.7)
Constipation	6 (1.9)	1 (0.3)	5 (1.5)	3 (0.9)	6 (3.1)	25 (4.1)	3 (1.5)
Diarrhoea	6 (1.9)	5 (1.6)	17 (5.2)	11 (3.3)	10 (5.1)	28 (4.6)	8 (4.1)

Source: Tables B.6-13 to B.6-19, pp.105-109 of the submission.

Abbreviations: AE, adverse event; SAE serious adverse event; URTI, upper respiratory tract infection.

* Includes events for dapagliflozin 2.5mg (n=202), 5mg (n=212) and 10mg (n=196) treatment arms.

6.17 Patients in the dapagliflozin trial (Wilding 2012) reported more adverse events and serious adverse events compared to other trials but event rates for dapagliflozin were comparable to placebo. Patients taking placebo in the sitagliptin Trial P260 reported more adverse events and serious adverse events compared to sitagliptin, consistent with higher doses of insulin taken. Patients taking sitagliptin in the sitagliptin Trial P051 reported more adverse events and serious adverse events compared with placebo. Overall, safety data in the clinical trials were not comparable due to differences in trial design and insulin titration protocols.

6.18 Patients treated with dapagliflozin reported statistically significantly more events suggestive of genital and urinary tract infections compared to placebo. Infections were more common in women, mostly occurred during the first 24 weeks of treatment, were mild or moderate in severity and responded to treatment.

6.19 There were substantial differences between trials in the proportions of patients experiencing hypoglycaemia events, consistent with the differences between trials in definitions of hypoglycaemia and insulin titration.

6.20 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. However, a subsequent FDA review of these data (14 April 2015) found the cardiovascular risk of saxagliptin was acceptable. Results of the Trial Evaluating Cardiovascular Outcomes with Sitagliptin study (TECOS; NCT00790205) released 28 April 2015 (http://www.merck.com/mrl/clinical_trials/outcomes_study.html) showed no increase in hospitalisations for heart failure associated with use of sitagliptin. There are no current TGA safety alerts for sitagliptin.

- 6.21 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 (click on the following link: FDA warning). The European Medicines Agency's Pharmacovigilance Risk Assessment Committee has recently commenced a review of SGLT2 inhibitors to evaluate the risk of diabetic ketoacidosis (click on the following link: EMA review).

Clinical claim

- 6.22 The submission described sitagliptin as non-inferior in terms of comparative effectiveness, similar in terms of reduction in mean daily insulin dose and similar in terms of comparative safety compared to dapagliflozin. The evaluation considered this claim was adequately supported in terms of comparative efficacy and safety, but not in terms of reduction in mean daily insulin dose.
- The indirect comparisons presented in the submission demonstrated non-inferiority of sitagliptin 100mg compared to dapagliflozin 10mg in terms of reduction in HbA1c over 24 weeks.
 - Given substantial differences in baseline insulin doses and insulin management regimens between trials, the sitagliptin (P260) and dapagliflozin (Wilding 2012) trials presented in the submission were not comparable in terms of reduction in mean daily insulin dose. In Trial P260 the addition of sitagliptin 100mg to insulin regimens resulted in an increased mean daily insulin dose (+19.0IU/day) over 24 weeks, while in Wilding 2012 the addition of dapagliflozin 10mg resulted in a reduced mean daily insulin dose (-1.18IU/day).
 - The submission stated that both sitagliptin 100mg and dapagliflozin 10mg were well tolerated and had different safety profiles with similar impacts on patient relevant outcomes. However, the submission also noted that dapagliflozin was associated with an increased incidence of genital infections requiring treatment, particularly in women.
- 6.23 The PBAC considered that the claim of non-inferior comparative effectiveness may not be reasonable in terms of reduction in HbA1c. The PBAC considered that the results of Trial P051 were not informative given that the trial did not allow insulin titration. The PBAC noted that treatment with sitagliptin was associated with a small decrease in HbA1c in Trial P260 (which allowed insulin to be adjusted), but that this was a secondary outcome of the trial.
- 6.24 The PBAC did not consider the claim of non-inferiority was reasonable in terms of reduction in mean daily insulin dose, noting that the addition of sitagliptin to insulin regimens resulted in an increased mean daily insulin dose.

- 6.25 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

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

Economic analysis

- 6.26 The submission presented a cost-minimisation analysis. The equi-effective doses were sitagliptin 100mg once daily and dapagliflozin 10mg daily. These estimates were trial based and agreed by the PBAC when dapagliflozin was recommended for dual therapy in T2DM (dapagliflozin PSD, July 2013).

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

Drug cost/patient/year

- 6.27 At the requested DPMQ of \$59.20 for a 28 tablet pack of 25 mg, 50 mg or 100 mg sitagliptin, the drug cost/patient/year was \$771.97 (assuming 13.04 packs per year). The drug cost/patient/year for the sitagliptin+metformin fixed dose combinations ranged from \$796.09 to \$818.52 (with requested DPMQs ranging from \$61.05 to \$62.77, depending on combination dose strengths, and assuming 13.04 packs per year). By comparison, the drug cost/patient/year for a 28 tablet pack of dapagliflozin 10 mg was \$764.93 (at the DPMQ of \$58.66, assuming 13.04 packs per year). The difference in price between sitagliptin and dapagliflozin (\$0.46 at ex-manufacturer prices) is due to the cost associated with monitoring and treating higher rates of adverse events such as genital mycotic infections and urinary tract infections with dapagliflozin.

Estimated PBS usage & financial implications

- 6.28 This submission was not considered by DUSC. The submission presented a market share approach, with estimates based on extrapolated trends of sitagliptin use in combination with insulin (\pm metformin) outside its listed restriction derived from an analysis of the 10% Medicare sample data (Jan 2010-Mar 2014).
- 6.29 The submission estimated the utilisation of sitagliptin, sitagliptin fixed dose combination products, dapagliflozin and dapagliflozin+metformin concomitant regimens for "sitagliptin listed" and "sitagliptin not listed" scenarios. The listed and not listed scenario estimates were compared and the difference presented as the incremental utilisation of sitagliptin in combination with insulin.
- 6.30 The submission assumed that in the not listed scenario, 80% of patients would add dapagliflozin and 20% would add sitagliptin to existing insulin regimens. If the sitagliptin listing was extended, it was assumed that 50% of patients would add dapagliflozin and 50% would add sitagliptin to existing insulin regimens.
- 6.31 The estimated cost to the PBS was then calculated for the incremental population, assuming a distribution across sitagliptin and sitagliptin+metformin fixed dose combinations derived from the 10% Medicare sample analysis. The same methodology was used to estimate the cost offsets for substitution of dapagliflozin and dapagliflozin + metformin concomitant regimens. The impact and substitution of

other diabetes medicines used in combination with insulin (e.g. pioglitazone and exenatide) was not considered.

Table 6: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients using sitagliptin in combination with insulin ± metformin (not listed)					
Sitagliptin + insulin ± metformin ^a					
Add sitagliptin to insulin + metformin					
Total patients (not listed)					
Patients using sitagliptin in combination with insulin ± metformin (listed)					
Sitagliptin + insulin ± metformin ^a					
Add sitagliptin to insulin + metformin					
Total patients (listed)					
Incremental difference in number of patients (listed - not listed) and total scripts					
Incremental number of patients					
Total incremental scripts ^b					
Cost of listing sitagliptin to the PBS					
Incremental cost of sitagliptin to PBS (DPMQ)	\$	\$	\$	\$	\$
Patient co-payment	\$	\$	\$	\$	\$
Incremental cost of sitagliptin (less co-payment)	\$	\$	\$	\$	\$
Incremental savings to the PBS from substitution of dapagliflozin and metformin					
Savings from dapagliflozin (DPMQ)	\$	\$	\$	\$	\$
Savings from metformin (DPMQ)	\$	\$	\$	\$	\$
Total savings to PBS (DPMQ)	\$	\$	\$	\$	\$
Total savings to PBS (less co-payment)	\$	\$	\$	\$	\$
Net incremental cost of listing sitagliptin to PBS					
Net incremental cost (DPMQ)	\$	\$	\$	\$	\$
Net incremental cost (less co-payment)	\$	\$	\$	\$	\$
Net cost of listing sitagliptin to PBS (listed)^c					
Net cost (DPMQ)	\$	\$	\$	\$	\$
Net cost (less co-payment)	\$	\$	\$	\$	\$

Source: Tables E.4-2, p.128, E.5-5, p.130, E.7-1, p.132, E.7-5, p.135, E.8-4, p.137, E.8-5, p.137, E.9-4, p.152, E.10-2, p.142, E.11-2, p.146, E.11-3, p.146 of the submission.

^a Estimated prevalent population taking sitagliptin in combination with insulin outside the restriction, with an assumed 30% attrition rate.

^b Total scripts were distributed across doses and formulations.

^c Total net costs of patients treated with sitagliptin if listed on the PBS, including patient switching from out of restriction use, compiled during the evaluation.

The redacted table above shows that at year 5, the estimated number of patients was less than 10,000 and the net cost to the PBS would be less than \$10 million.

- 6.32 It was unclear if the counts of patient numbers derived from the 10% Medicare sample analysis were extrapolated to the full Australian population or represent 10% of that population. The number of eligible patients may have been substantially underestimated. The PSCR confirmed that the 10% Medicare sample was extrapolated to represent the full Australian population.
- 6.33 The assumed attrition rate of 30% was not supported and application to both listed and not listed scenarios was not adequately justified.

- 6.34 The estimated number of patients adding sitagliptin to existing insulin + metformin regimens for the year ending March 2014 (less than 10,000) derived from the 10% Medicare sample analysis could not be verified, and was substantially lower than the average number of patients taking sitagliptin in combination with metformin over the same period (less than 10,000).
- 6.35 The assumption that 80% of patients currently adding sitagliptin to insulin + metformin regimens would switch to dapagliflozin if sitagliptin is not listed for combination with insulin was not reasonable. The submission noted that dapagliflozin was recently listed for use in combination with insulin (April 2015 PBS schedule). However, the use of sitagliptin in combination with insulin has increased over time despite not being listed on the PBS schedule for this restriction. Similarly, the assumption dapagliflozin and sitagliptin would be used on a 1:1 ratio in combination with insulin, was not supported.
- 6.36 The submission assumed that extending the listing of sitagliptin to include combination with insulin would not increase the market size, and that all patients adding sitagliptin to insulin regimens would otherwise have added dapagliflozin. Given the different modes of action and safety profiles between sitagliptin and dapagliflozin this assumption was not supported.
- 6.37 Assumptions around the number of patients continuing sitagliptin in combination with insulin, and adding sitagliptin or dapagliflozin to insulin + metformin regimens, resulted in a reduction in the utilisation of sitagliptin in combination with insulin from Year 1 to Year 5 in the not listed scenario, and from Year 1 to Year 3 in the listed scenario. A reduction in sitagliptin utilisation was not reasonable in either scenario. The estimates of financial implications to government were highly uncertain and should not be relied on.

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

Quality Use of Medicines

- 6.38 The sponsor has developed educational materials supporting the appropriate use of diabetes medicines in clinical practice.

7 PBAC Outcome

- 7.1 The PBAC did not recommend listing sitagliptin, sitagliptin+metformin and sitagliptin+metformin XR in combination with insulin for T2DM on the PBS. In making its recommendation, the PBAC considered that the clinical need and place of therapy were not well defined and the clinical effectiveness (in terms of reduction in mean daily insulin dose) was uncertain.
- 7.2 Based on the data provided, the PBAC did not accept that there was a clinical place in therapy for sitagliptin in combination with insulin. In making this decision, the PBAC noted that while sitagliptin resulted in a small statistically significant decrease in HbA1c, the addition of sitagliptin to insulin regimens resulted in an increased mean

daily insulin dose. The PBAC considered that clinicians would be unlikely to prescribe a drug that resulted in increased insulin use.

- 7.3 The PBAC considered that dapagliflozin was the appropriate comparator. The PBAC noted that exenatide and insulin up-titration would have been appropriate secondary comparators but were not considered in the submission.
- 7.4 The PBAC recalled that it had recommended dapagliflozin in combination with insulin for the treatment of T2DM at its November 2014 meeting. The recommendation was formed on the basis of a cost-minimisation and cost-analysis derived from the costs of insulin up-titration avoided.
- 7.5 The PBAC considered that the clinical trials presented in the submission did not provide adequate data to support the clinical claim that sitagliptin is non-inferior in terms of comparative effectiveness (as measured by reduction in HbA1c) and similar in terms of reduction in mean daily insulin dose compared to dapagliflozin.
- The PBAC considered that it was not appropriate to include trial P051 in the indirect analysis assessing change from baseline in HbA1c, as the insulin dose was unable to be titrated. The PBAC noted this was not consistent with clinical practice.
 - The PBAC agreed with the ESC that trials P260 and Wilding 2012 were not comparable in terms of reduction in mean daily insulin dose due to substantial differences in baseline insulin doses and insulin management regimens. However, the addition of sitagliptin to insulin regimens resulted in an increased mean daily insulin dose while the addition of dapagliflozin resulted in a reduced mean daily insulin dose (see paragraph 6.22).
- 7.6 The PBAC did not accept the sponsor's argument in the pre-PBAC response that sitagliptin would result in insulin up-titration avoided of between 26.5IU and 28.2IU (see paragraph 6.10).
- 7.7 The PBAC considered that sitagliptin 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 increased daily insulin dose accompanying sitagliptin treatment (+19.0IU/day, compared with -1.18IU/day for dapagliflozin) was not factored into the cost-minimisation analysis. If the PBAC accepted that sitagliptin with insulin and dapagliflozin with insulin were non-inferior in terms of reduction in HbA1c, the cost of this outcome would be greater for patients on sitagliptin with insulin given the greater dose of insulin required. The PBAC considered that this cost should have been factored into the cost-minimisation analysis.
- 7.9 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 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.

9 Sponsor's Comment

The sponsor had no comment.