

**6.05 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 To request Authority Required (Streamlined) listing for sitagliptin for the treatment of type 2 diabetes mellitus (T2DM) as part of triple oral therapy with metformin (MET) and a sulfonylurea (SU). The submission also requested that the sitagliptin/MET and sitagliptin/MET XR fixed dose combinations (FDCs) be listed for triple oral therapy with a SU.

2 Requested PBS 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	№.of Rpts	Proprietary Name and Manufacturer	
SITAGLIPTIN sitagliptin 25 mg tablet, 28 sitagliptin 50 mg tablet, 28 sitagliptin 100 mg tablet, 28	1	5	Januvia®	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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<p>Clinical criteria:</p>	<p>The treatment must be in combination with metformin,</p> <p>AND</p> <p>The treatment must be in combination with a sulfonylurea,</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 either metformin or a sulfonylurea or metformin and sitagliptin or a sulfonylurea and sitagliptin <i>maximally tolerated doses of metformin and a sulfonylurea;</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 either metformin or a sulfonylurea or metformin and sitagliptin or a sulfonylurea and sitagliptin <i>maximally tolerated doses of metformin and a sulfonylurea.</i></p>
<p>Prescriber Instructions</p>	<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> <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 sitagliptin <i>this drug.</i></p>
<p>Administrative Advice</p>	<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>

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary and Manufacturer	Name
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® Janumet XR®	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				

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)
Clinical criteria:	<p>The treatment must be in combination with metformin,</p> <p>AND</p> <p>The treatment must be in combination with a sulfonylurea,</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 either metformin or a sulfonylurea or metformin and sitagliptin or a sulfonylurea and sitagliptin <i>maximally tolerated doses of metformin and a sulfonylurea;</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 either metformin or a sulfonylurea or metformin and sitagliptin or a sulfonylurea and sitagliptin <i>maximally tolerated doses of metformin and a sulfonylurea.</i></p>

<p>Prescriber Instructions</p>	<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: (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 an 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 sitagliptin <i>this drug</i>.</p>
<p>Administrative Advice</p>	<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 listing was requested on a cost-minimisation basis compared to dapagliflozin, assuming that cost-offsets applied in the PBS dual therapy listing will apply to the listing of dapagliflozin and sitagliptin when used in triple oral therapy.
- 2.3 The Pre-PBAC response raised concerns that the proposed changes to the restriction wording do not appear to be equitable or clinically appropriate. The current PBS restriction for sitagliptin allows patients uncontrolled on MET or SU monotherapy to add sitagliptin (dual oral therapy). The sponsor argued that the proposed restriction wording would restrict access to triple oral therapy, with sitagliptin, MET and a SU, to only those patients who have first trialed and failed the combination of MET and a SU, excluding those patients uncontrolled on dual oral therapy with sitagliptin from moving to triple oral therapy. The Pre-PBAC response further noted that the only treatment pathway available to these patients would be to stop sitagliptin treatment, add in a SU or MET, and then add back in sitagliptin, which would be considered clinically inappropriate.

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

3 Background

- 3.1 **TGA status at time of PBAC consideration:** Sitagliptin was approved for registration by the TGA on 5 June 2013 as triple combination therapy with MET and a SU when combination therapy with both agents does not provide adequate glycaemic control.

- 3.2 Sitagliptin was considered by the PBAC at the March 2008 meeting, and recommended for listing as an Authority required (STREAMLINED) benefit for the treatment of T2DM as part of dual oral combination therapy with MET or a SU, on the basis of a cost minimisation analysis versus rosiglitazone.
- 3.3 Sitagliptin+MET XR was considered by the PBAC at the November 2013 meeting, and recommended for listing as an Authority required (STREAMLINED) benefit for the treatment of T2DM for patients inadequately controlled on MET alone, on the basis of bioequivalence with the individual components.
- 3.4 This was the PBAC's first consideration of sitagliptin and the sitagliptin/MET FDCs for triple oral therapy in T2DM.

4 Clinical place for the proposed therapy

- 4.1 T2DM as triple oral therapy in combination with MET and a SU when therapy with both agents does not provide adequate glycaemic control. Alternative agents for triple therapy (+MET+SU) include oral therapies pioglitazone, dapagliflozin and other DPP-4 inhibitors or injection therapies (insulin and exenatide).

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

5 Comparator

- 5.1 The PBAC recommended the listing of dapagliflozin for the treatment of T2DM in combination with MET and a SU (referred to as triple oral therapy) at the March 2015 meeting. Therefore dapagliflozin was considered an appropriate comparator for a listing of sitagliptin in combination with MET and a SU for triple oral therapy. The submission did not include a comparison of sitagliptin with injection formulations insulin glargine or exenatide which might be comparators in the absence of listing of dapagliflozin.

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 an indirect comparison with placebo+MET+SU as common comparator:

- Sitagliptin+MET+SU versus placebo+MET+SU (meta-analysis of P035 & P229).
- Dapagliflozin+MET+SU versus placebo+MET+SU (Matthaei 2015).

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
Sitagliptin vs. placebo, both in combination with metformin and a sulfonylurea		
P035 (Phase A, Stratum 2* patients)	Clinical Study Report Protocol 035V1 A Multicentre, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate Safety and Efficacy of the Addition of MK-0431 to Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycaemic Control on Glimperide Alone or in Combination With Metformin. Hermansen K; Kipnes, M; Luo, E; Fanurik, D; Khatami, H; and Stein P for the Sitagliptin Study 035 Group (2007) Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin.	6 October 2006 Diabetes, Obesity and Metabolism, 9, 2007, 733–745
P229	A Phase III, Randomised, Clinical Trial to Evaluate the Safety and Efficacy of the Addition of Sitagliptin in Patients with Type 2 Diabetes Mellitus Who Have Inadequate Glycaemic Control on a Sulphonylurea in Combination With Metformin.	14 May 2012
Dapagliflozin vs. placebo, both in combination with metformin and a sulfonylurea		
Matthaei 2015	Matthaei S, Bowering K, Rohwedder K, Grohl A, Parikh S for the Study 05 Group, Dapagliflozin improves glycaemic control and reduces body weight as add-on therapy to metformin plus sulphonylurea: A 24-week randomised, double-blind clinical trial.	Diabetes Care; Published online ahead of print 15 January 2015

*Stratum 2 were taking metformin+sulfonylurea; Stratum 1 were taking sulfonylurea alone.
Source: Table B.2-2, page 57 of the submission

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

Table 2: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Sitagliptin 100mg vs placebo as add-on therapy to metformin and sulfonylurea					
P035	229	RCT, DB, MC 24 weeks	Low	T2DM aged ≥18 and ≤75 years HbA1c ≥7.5% and ≤10.5% Glimepiride ≥4 mg/day + metformin ≥1500 mg/day; open-label rescue pioglitazone	HbA1c, FPG, 2-hour PPG
P229	427	RCT, DB, MC 24 weeks	Low	T2DM aged ≥18 and ≤78 years HbA1c ≥7.5% and ≤10.5% Glimepiride ≥2 mg/day or gliclazide ≥60 mg daily of modified release formulation or ≥160 mg/day non-modified release formulation + metformin ≥1500 mg/day Open-label rescue pioglitazone	HbA1c, FPG, 2-hour PPG
Meta-analysis	656	Included P035, P229			HbA1c
Dapagliflozin 10mg vs placebo as add-on therapy to metformin and sulfonylurea					
Matthaei	218	RCT, DB, MC 24 weeks	Low	T2DM aged ≥18 with T2DM HbA1c ≥7.0% and ≤10.5% Stable metformin ≥1500mg/day and maximum tolerated dose of sulfonylurea (at least 50% of maximum dose)	HbA1c, FPG

Abbreviations: DB double-blind; FPG fasting plasma glucose; HbA1c Glycosylated haemoglobin; MC multi-centre; PPG post-prandial glucose; RCT randomised controlled trial; T2DM type 2 diabetes mellitus.

Source: Table B.2-3, pp 58-61 of the submission

Comparative effectiveness

6.6 The results of the indirect comparison are shown in Table 3.

Table 3: Mean change in HbA1c from baseline to week 24: sitagliptin vs placebo, dapagliflozin vs placebo as add-on therapy to metformin and sulfonylurea

Trial ID	Comparison	Week; population	LS mean change from baseline (95% CI)		Difference in LS mean change (95% CI)
			Active treatment	Placebo	
P035	Sitagliptin vs placebo	24; APT	-0.59 (-0.74, -0.44)	0.30 (0.14, 0.45)	-0.89 (-1.10, -0.68)
P229	Sitagliptin vs placebo	24; FAS	-0.84 (-0.97, -0.71)	-0.16 (-0.28, -0.03)	-0.68 (-0.87, -0.50)
Meta-A	Sitagliptin vs placebo	24	Pooled estimate trials P035, P229		-0.78 (-0.92, -0.64)
Matthaei	Dapagliflozin vs placebo	24; FAS	-0.86 (-1.0, -0.72)	-0.17 (-0.31, -0.02)	-0.69 (-0.89, -0.49)
Indirect comparisons					
Sitagliptin (pooled) vs dapagliflozin					- 0.09 (-0.33, 0.15)
Sitagliptin (P035) vs dapagliflozin					- 0.20 (-0.49, 0.09)
Sitagliptin (P229) vs dapagliflozin					0.01 (-0.26, 0.28)

Source: Table B.6-1, B.6-2, pp 88-90 of the submission

Abbreviations: APT All patients treated; CI, Confidence interval; FAS full analysis set; HbA1c, Glycosylated haemoglobin; LS least squares; Meta-A meta-analysis of trials P035 and P229

6.7 The results of the indirect analyses were consistent with no statistically significant differences between sitagliptin and dapagliflozin in reduction in HbA1c at 24 weeks. The observed differences were within the minimally important clinical difference (MCID) of 0.3% - 0.4% previously accepted by the PBAC (Dapagliflozin PSD, March 2015 meeting).

- 6.8 No evidence was presented supporting the comparative efficacy of sitagliptin 25mg and 50mg strengths or sitagliptin/MET FDCs (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 FDCs.

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

Comparative harms

- 6.9 A summary of key adverse events reported in the trials is provided in Table 4.

Table 4: Summary of adverse events reported in sitagliptin and dapagliflozin trials

Number (%) of patients	P035 (Stratum 2)*		P229 (Phase A)*		Matthaei 2015	
	SITA	Placebo	SITA	Placebo	DAPA	Placebo
With ≥1 adverse events	73 (62.9)	60 (53.1)	91(43.3)	81 38.2)	53 (48.6)	56 51.4)
Drug-related adverse events	21 (18.1)	8 (7.1)	13 (6.2)	5 (2.4)	18 (16.5)	8 (7.3)
Serious adverse events	7 (6.0)	2 (1.8)	2 (1.0)	6 (2.8)	1 (0.9)	6 (5.5)
Deaths	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Discontinued due adverse events	2 (1.7)	2 (1.8)	2 (1.0)	3 (1.4)	2 (1.8)	3 (2.8)
Drug-related discontinuations	0 (0.0)	1 (0.9)	1 (0.5)	1 (0.5)	NR	NR
Discontinued serious events	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.5)	NR	NR
Hypoglycaemia						
Overall	19 (16.4)	1 (0.9)	31(14.8)	10 (4.7)	14 (12.8)	4 (3.7)
Requiring non-medical assistance	2 (1.7)	0	0	0	0	0
Requiring medical assistance	0	0	1 (0.5)	0	0	0
Genital infection overall	NR	NR	NR	NR	6 (5.5)	0
Men					1/46 (2.2)	0
Women					5/63 (7.9)	0
Urinary tract infection	2 (1.7)	1 (0.9)	NR	NR	5 (4.6)	7 (6.4)
Bronchitis	2 (1.7)	2 (1.8)	3 (1.4)	1 (0.5)	5 (4.6)	1 (0.9)
Upper respiratory tract infection	8 (6.9)	9 (8.0)	8 (3.8)	12 (5.7)	NR	NR

Abbreviations: SITA sitagliptin; DAPA dapagliflozin

*P035 Phase A, Stratum 2 excluding data after initiation of glycaemic rescue therapy; P229 Phase A, excluding data after initiation of glycaemic rescue therapy

Source: Tables B.6-5, B.6-10, B.6-11, B.6-12 pages 96, 99,100 of the submission

- 6.10 Both sitagliptin and dapagliflozin were associated with more hypoglycaemia than placebo. Generally the hypoglycaemia did not require either non-medical or medical assistance. Dapagliflozin was associated with more genital tract and urinary tract infections than placebo.

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

Benefits/harms

- 6.11 On the basis the indirect evidence presented in the submission, the comparison of sitagliptin and dapagliflozin resulted in:
- No clinically important difference between sitagliptin and dapagliflozin in terms of reduction in HbA1c during a maximum duration of exposure of 24 weeks. A reduction of 0.3%-0.4% in HbA1c is the MCID.

- There were no statistically significant differences in the proportion of patients experiencing at least one adverse event, or any hypoglycaemic event between those treated with sitagliptin + MET + SU and those treated with dapagliflozin + MET + SU.
- 6.12 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.
- 6.13 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

- 6.14 The submission described sitagliptin as non-inferior in terms of comparative effectiveness and similar in terms of comparative safety over dapagliflozin. This claim was adequately supported.
- Sitagliptin and dapagliflozin produced comparable reductions in HbA1c when used in conjunction with MET and a SU in T2DM;
 - Rates of adverse events and serious adverse events were similar; dapagliflozin was associated with more genital infections requiring management and treatment.
- 6.15 The PBAC considered that the claim of non-inferior comparative effectiveness to dapagliflozin was reasonable.
- 6.16 The PBAC noted that sitagliptin has a different safety profile to dapagliflozin but considered the claim of similar comparative safety to dapagliflozin was reasonable.

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

Economic analysis

- 6.17 Cost-minimisation analysis. The equi-effective doses are 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).

Drug cost/patient/year

6.18 At the DPMQ requested in the submission (as per the then current listed DPMQ for sitagliptin), 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+MET 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

6.19 This submission was not considered by DUSC. A market share approach was used. Data from a 10% Medicare sample provided the basis of market projections, patterns of use of sitagliptin fixed dose combination products and likely substitution patterns. The estimates were based on assumptions about the relative costs of dapagliflozin and sitagliptin and uptake patterns of triple oral therapy in clinical practice. Estimates of numbers of patients, numbers of units and net costs to PBS/RPBS/MBS are shown in Table 5.

Table 5: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use (numbers of patients)					
Number treated (current triple with SITA)					
Market share of new triple (add to MET+SU)	%	%	%	%	%
New to triple therapy with SITA					
Market share triple (add SU to MET+SITA)	%	%	%	%	%
New to triple therapy with SU added					
Total new to triple therapy with SITA					
Scripts^a Estimated units of use					
Total increased units (increased SITA, SU)					
Total decreased units (reduced DAPA, MET)					
Net change units (increased – decreased)					
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
Net cost to MBS*	-\$	-\$	-\$	-\$	-\$
Estimated total net cost					
Net cost to PBS/RPBS/MBS	\$	\$	\$	\$	\$

^a Scripts are distributed across sitagliptin, sitagliptin+metformin, sitagliptin+metformin XR items

*Submission assumes small cost savings due to fewer genital mycotic infections with decreased dapagliflozin use, however these are ignored in calculation of net costs to PBS/RPBS

Abbreviations: SITA sitagliptin; MET metformin; SU sulfonylurea; DAPA dapagliflozin

Source: Table E.12-1p 143 of the submission; Excel Worksheets Net cost to PBS, Cost to Govt for MBS [file Triple Section E]

- 6.20 The redacted table above shows that at year 5, the estimated number of packs was between 10,000 - 50,000 and the net cost to the PBS/RPBS would be less than \$10 million.

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of sitagliptin and the sitagliptin/MET FDCs for the treatment of T2DM in combination with MET and a 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 sitagliptin 100mg and dapagliflozin 10mg.
- 7.2 The PBAC accepted that sitagliptin used in combination with MET and a SU, or sitagliptin/MET FDC in combination with 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 recalled that it recommended the sitagliptin/MET FDCs at its November 2013 meeting, on the basis that the FDCs were similar in efficacy and safety to the co-administration of the same doses of the individual components.
- 7.4 The PBAC acknowledged the sponsor's comments regarding the proposed changes to the restriction wording and agreed that the original wording requested by the sponsor was clinically appropriate. The PBAC further recommended that the restriction wording for other DPP-4 inhibitors and SGLT2 inhibitors listed for triple oral therapy in T2DM should be changed for consistency with the sitagliptin listing. The PBAC recommended the following wording to replace the words at the end of this clinical criterion: "...despite treatment with either metformin or a SU or metformin and ~~sitagliptin this drug~~ or a SU and ~~sitagliptin this drug~~". The changes to the wording requested by the submission (with suggested additions in italics and deletions crossed out with strikethrough) would allow for this criterion to be used in the restriction for all triple oral therapy T2DM drugs.
- 7.5 The PBAC considered there was a clinical place for sitagliptin 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 requesting listing for sitagliptin in combination with MET, a SU 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 considered that dapagliflozin (in combination with MET and a SU) was the appropriate comparator.
- 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 advised the Minister that under Section 101(3BA) of the National Health Act 1953:

- sitagliptin should be treated as interchangeable on an individual patient basis with saxagliptin for triple oral therapy for T2DM; and
- sitagliptin/MET FDC should be treated as interchangeable on an individual patient basis with saxagliptin/MET FDC for triple oral therapy for T2DM.

- 7.9 The PBAC advised that the NOTE in the current restriction for sitagliptin and the sitagliptin/MET FDCs in dual therapy will need to be amended to allow for triple oral combination therapy.
- 7.10 The PBAC advised that sitagliptin and the sitagliptin/MET FDCs are suitable for prescribing by nurse practitioners within collaborative arrangements.
- 7.11 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	
SITAGLIPTIN sitagliptin 25 mg tablet, 28 sitagliptin 50 mg tablet, 28 sitagliptin 100 mg tablet, 28	1	5	Januvia®	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)

Public Summary Document – July 2015 PBAC Meeting

<p>Clinical criteria:</p>	<p>The treatment must be in combination with metformin,</p> <p>AND</p> <p>The treatment must be in combination with a sulfonylurea,</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 either metformin and a sulfonylurea, or metformin and this drug, or a sulfonylurea and this drug;</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 either metformin and a sulfonylurea, or metformin and this drug, or a sulfonylurea and this drug.</p>
<p>Prescriber Instructions</p>	<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> <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>
<p>Administrative Advice</p>	<p>Note</p> <p>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>

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary and Manufacturer	Name
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				
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® 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)
Clinical criteria:	<p>The treatment must be in combination with a sulfonylurea,</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 either metformin and a sulfonylurea, or metformin and this drug, or a sulfonylurea and this drug;</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 either metformin and a sulfonylurea, or metformin and this drug, or a sulfonylurea and this drug.</p>

<p>Prescriber Instructions</p>	<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> <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 fixed dose combination.</p>
<p>Administrative Advice</p>	<p>Note</p> <p>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.