

**7.15 SITAGLIPTIN, tablet, 100 mg, 50 mg, 25 mg, Januvia®
SITAGLIPTIN and METFORMIN, tablet, 50/500mg, 50/850mg,
50/1000mg, Janumet®
SITAGLIPTIN and METFORMIN XR, tablet, 50/1000mg,
100/1000mg, Janumet XR®
Merck Sharp & Dohme (Australia) Pty Ltd**

1 Purpose of Application

- 1.1 The minor re-submission requested an extension of the current Authority Required (STREAMLINED) listings of the Januvia®, Janumet® and Janumet® XR for use in combination with insulin in patients with type 2 diabetes, with or without metformin.

2 Requested listing

- 2.1 The July 2015 major submission requested the following new listing. 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®	MSD
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®	MSD
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®	MSD

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 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>
<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>Administrative Advice</p>	<p><u>Note:</u> <i>Continuing Therapy Only:</i> <i>For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner.</i> <i>Further information can be found in the Explanatory Notes for Nurse Practitioners.</i></p> <p><u>Note</u> <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>

3 Background

3.1 The requested listing was previously considered as a major submission by the PBAC in July 2015.

3.2 The major submission was rejected on the basis 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.

3.3 Specifically, from the July 2015 PBAC Minutes:

- [T]he 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. (Para 7.2)
- 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. (Para 7.5)
- 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. (Para 7.6)
- 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. (Para 7.8)

3.4 The sponsor elected to clarify the design and outcomes of trial P260 (treat-to-target trial) and the relationship of this trial to P051 and Wilding through a minor re-submission.

4 Clinical place for the proposed therapy

4.1 The clinical place in therapy was unchanged from the July 2015 major submission

5 Comparator

- 5.1 The previous major submission considered by the PBAC in July 2015 nominated dapagliflozin as the comparator. This was unchanged in the minor re-submission as the PBAC had considered it appropriate. The PBAC had also noted that exenatide and insulin up-titration would have been appropriate secondary comparators but were not considered in the submission.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item as it was a minor submission.

Consumer comments

- 6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

- 6.3 As a minor submission, no new clinical trials were presented in the re-submission.
- 6.4 The basis of the minor submission's request was to review and better describe the clinical evidence as presented in the previous major submission.
- 6.5 The PBAC noted that the minor resubmission took the position that the Committee should disregard the comparison between trials P260 and Wilding. The PBAC recalled its July 2015 conclusion 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.

Comparative effectiveness

- 6.6 The trial results remained unchanged from the previous major submission considered in July 2015. The minor re-submission summarised its approach to previous PBAC concerns as per Table 1.

Table 1: Minor resubmission’s summary of key issues, approach to address the issue and summary of outcomes

Issue	Approach	[Sponsor’s] Conclusion
<p>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.</p> <p>(PBAC Minutes, para 7.5)</p> <p>See Section D.1 of minor re-submission</p>	<p>Review comparability of the key trial characteristics of P051 and Wilding including the insulin dosing management</p> <p>Review relevance of a stable insulin dose in both trials to decision making</p> <p>Summary of key outcomes from both trials and analysis of non-inferiority based on mean change in HbA1c</p>	<p>P051 is the appropriate key trial to compare with Wilding</p> <p>The indirect analysis of P051 to Wilding supports the non-inferiority claims presented in the submission</p> <p>All key trial characteristics of P051 and Wilding are the same and comparable including the insulin dosing requirements.</p> <p>Both trials are registration studies. Regulatory guidelines require the insulin dose to be held steady (+/-10%) to allow the incremental benefit of adding sitagliptin or dapagliflozin to insulin to be demonstrated</p> <p>PBAC has previously accepted that trials with stable insulin doses are suitable for decision making, e.g. Wilding formed the basis of the dapagliflozin positive recommendation.</p> <p>The indirect analysis met the test for non-inferiority</p>
<p>The addition of sitagliptin to insulin regimens resulted in an increased mean daily insulin dose.</p> <p>(PBAC Minutes, para 7.2)</p>	<p>Review insulin dose changes in pivotal P051 and Wilding trials</p> <p>Review trial design and results of P260</p> <p>Describe difference in trial design between P260 treat-to-target trial and the registration studies of P051 and Wilding</p> <p>Compare the key outcomes from P260 to P051 and Wilding</p>	<p>Sitagliptin does not result in an increased mean daily insulin dose</p> <p>There was no significant increase in insulin dose between the sitagliptin and placebo arm of P051.</p> <p>The insulin dose changes in P051 and Wilding were comparable</p> <p>P260 is a treat-to-target trial with a forced insulin titration schedule</p> <p>Patients in both study arms were required to increase their insulin dose to reach a set glycaemic target</p> <p>In P260, patients in the sitagliptin + insulin titration arm had significantly better glycaemic control than patients in the insulin up-titration only arm</p> <p>Patients in the sitagliptin arm used <u>less insulin</u>, not more, than patients in the placebo arm and experienced significantly less hypoglycaemia and less weight gain</p> <p>The reduction in HbA1c in the sitagliptin arm of P260 was significantly better than the sitagliptin arm of P051 or the dapagliflozin arm of Wilding.</p>

Issue	Approach	[Sponsor's] Conclusion
Clinical need and place in therapy of sitagliptin in combination with insulin (PBAC Minutes, para 7.1)	Review clinical implications of P260 results Review safety profile including current TGA warnings relating to SGLT-2 inhibitors Review clinical benefits of sitagliptin in this context	There is a high clinical need for sitagliptin use in combination with insulin There is significant clinical need for diabetes therapies that reduce the harms associated with insulin up-titration while improving glycaemic control. This need is matched by the clinical profile of sitagliptin Clinicians desire options for treating patients with insulin Importantly SGLT-2 inhibitors are not suitable for all patients The efficacy of SGLT-2 drugs declines as renal insufficiency increases Not all patients can tolerate SGLT-2 inhibitors SGLT-2 inhibitors are associated with genital infections TGA has issued a warning that SGLT-2 inhibitors are associated with serious cases of ketoacidosis

Source: Minor resubmission, pp7-8.

- 6.7 The PBAC noted the minor resubmission's claim that the reduction in HbA1c in the sitagliptin arm of P260 was significantly better than the sitagliptin arm of P051 or the dapagliflozin arm of Wilding. The PBAC noted the comparison the across these three trials in table 2 below (reproduced from the July 2015 PBAC Minutes):

Table 2: 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.

- 6.8 The PBAC noted that despite the sponsor's claim that HbA1c reduction was significantly better in the sitagliptin arm of P260, the difference in LS mean change in HbA1c for the sitagliptin arm in P260 [-0.45 (-0.60, -0.29)] was lower than for the

sitagliptin arm of P051 [-0.56 (-0.7, -0.42)] and for the dapagliflozin 10mg arm of Wilding [-0.57 (-0.72, -0.42)].

Comparative harms

- 6.9 The comparative safety profile of sitagliptin remains unchanged from the previous major submission considered in July 2015. The PBAC previously 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.
- 6.10 The PBAC noted the sponsor's assertion that "... [p]atients in the sitagliptin arm... experienced significantly less hypoglycaemia and less weight gain..." than patients in the placebo arm.
- 6.11 The PBAC noted that in trial P051, "...the incidence of symptomatic hypoglycaemia was significantly ($p=0.003$) increased in patients treated with sitagliptin [16% (50/322)] compared with those treated with placebo [8% (25/319)]." The PBAC also noted that trial P051 reported that the, "...addition of sitagliptin to ongoing insulin therapy did not result in a significant change in body weight compared with placebo." The LS mean changes in body weight at week 24 from baseline were 0.1kg (-0.2, 0.4) for sitagliptin and 0.1kg (-0.3, 0.4) for placebo.
- 6.12 In contrast to the results of trial P051, the incidence of hypoglycaemia in P260 was lower in patients treated with sitagliptin (93, 28.3%) compared with placebo (144, 43.8%). The PBAC noted that no definition of hypoglycaemic events was given in P260. For change in body weight from baseline at week 24, trial P260 reported that, "...small increases in body weight were observed in both treatment groups, with a slightly greater increase in the placebo group, but with the 95% CI around the between-group difference including '0'".
- 6.13 Overall, the PBAC considered that the safety benefits of sitagliptin with regard to hypoglycaemia and weight gain were not consistent across the presented trials.

Clinical claim

- 6.14 The clinical claim remained unchanged from the previous major submission considered in July 2015. The previous submission claimed non-inferior comparative effectiveness and similar comparative safety of sitagliptin compared with dapagliflozin.
- 6.15 The PBAC considered in July 2015 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.

Economic analysis

- 6.16 In the previous major submission considered by PBAC in July 2015, the submission presented a cost-minimisation analysis against dapagliflozin. The equi-effective doses were sitagliptin 100mg once daily and dapagliflozin 10mg daily. 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". (PBAC July 2015 Minutes, para 7.8).
- 6.17 The minor re-submission did not alter the economic analysis from July 2015, but updated the analysis with the most current DPMQ prices for both drugs.

Drug cost/patient/year

- 6.18 At the updated requested DPMQ of \$ [REDACTED] for a 28 tablet pack of 25 mg, 50 mg or 100 mg sitagliptin, the drug cost/patient/year was \$ [REDACTED] (assuming 13.04 packs per year). The drug cost/patient/year for the sitagliptin+metformin fixed dose combinations ranged from \$ [REDACTED] to \$ [REDACTED] (with requested DPMQs ranging from \$ [REDACTED] to \$ [REDACTED], 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 \$ [REDACTED] (at the DPMQ of \$ [REDACTED], assuming 13.04 packs per year). The difference in price between sitagliptin and dapagliflozin (\$ [REDACTED] 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 In addition to the review of clinical evidence outlined above in Table 1, the sponsor noted that the PBAC had raised concerns about various assumptions used in the previous major submission's 'Estimated PBS usage & financial implications. [See PBAC July 2015 Minutes, paragraphs 6.32-6.37 for more detail]. In the minor submission the sponsor stated that some assumptions have been updated, and "[t]he additional data provides a more accurate representation of the expected financial impact".
- 6.20 The minor submission estimated a net cost to the PBS of \$ [REDACTED] in Year 5 of listing, with a total net cost to the PBS of \$ [REDACTED] less than \$10 million over the first 5 years of listing. Table 2 below outlines the expected PBS costs. In the re-submission, the following assumptions have been updated to address concerns raised in the July major submission:
- "Amending Sitagliptin and Dapagliflozin Dispensed Prices following the implementation of the 6th Community Pharmacy Agreement. They reflect the new pharmacy margins and dispensing fee taking effect from July 1st 2015.

- Raw data have been updated for patients 1) on SITA+INS (\pm MET), 2) on INS (\pm MET) and 3) Moved from INS (\pm MET). The Medicare 10% sample has been updated with data to September 2014 to reflect newer actual data from the sample. Linear forecasts from 2014 onwards are updated from the new baseline values.”

Table 3: Change in PBS costs expected as a result of listing sitagliptin, sitagliptin/metformin and sitagliptin/metformin XR (DPMQ less patient co-payments).

	Year 1	Year 2	Year 3	Year 4	Year 5
Increased use of SITA	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Decreased use of DAPA	\$366,261	\$734,314	\$1,136,479	\$1,572,756	\$2,043,147
Decreased use of MET	\$29,656	\$59,458	\$92,021	\$127,347	\$165,435
Total cost of drugs with decreased use	\$395,917	\$793,771	\$1,228,500	\$1,700,103	\$2,208,581
Net change (increased – decreased)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table F-3, p24 of the minor re-submission.

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

7 PBAC Outcome

- 7.1 The PBAC rejected the minor resubmission to extend the PBS listing for sitagliptin for use in combination with insulin in patients with type 2 diabetes, with or without metformin. The PBAC noted the sponsor’s arguments regarding the differences in trial design between trial P260 and Wilding. However, the PBAC did not consider that these arguments would support a position that a comparison between P260 and Wilding should be disregarded in assessing the clinical effectiveness of sitagliptin in combination with insulin.
- 7.2 The PBAC noted the resubmission’s claim that trial P051 “...is the appropriate key trial to compare with Wilding [and that]... [t]he indirect analysis of P051 to Wilding supports the non-inferiority claims presented in the submission.”
- 7.3 The PBAC noted that the design of P051 required the insulin dose to remain stable through the course of the trial, except for reductions to allow for hypoglycaemia and insulin dose adjustments for rescue therapy where progressively stricter glycaemic goals were not met. At the end of the trial, “...the overall mean change (\pm s.d.) in insulin dose from baseline was minimal, 0 IU (5.8) in the sitagliptin group and 1.6 IU (7.0) in the placebo.” (Vilsboll 2010, P051, Diabetes, Obesity and Metabolism 12: p170).
- 7.4 With regard to HbA1c improvement demonstrated in P051, the PBAC noted that patients on sitagliptin achieved a difference in least squares (LS) mean change of -0.6 (-0.7, -0.4) compared with patients on placebo (Vilsboll 2010, P051, Diabetes, Obesity and Metabolism 12: p172).

- 7.5 The PBAC noted that P260 was designed to evaluate the difference in the change from baseline in insulin dose between sitagliptin and placebo, with the primary efficacy endpoint being the change from baseline in daily insulin dose at 24 weeks.
- 7.6 With regard to change in daily insulin dose at week 24 from baseline demonstrated in P260 the PBAC noted patients on sitagliptin had an LS mean change of 19.0 IU (16.5, 21.6) compared with 23.8 (21.3, 26.3) for patients on placebo (P260 Clinical Study Report). For the secondary outcome of change from baseline HbA1c, the PBAC noted a difference in LS mean of -0.45 (-0.60, -0.29).
- 7.7 The PBAC noted that the trial design of Wilding 2012, comparing dapagliflozin with placebo, held daily insulin doses constant (within 10% of baseline dose), with up- and down-titration of insulin dose permitted for patient wellbeing (based on HbA1c and fasting blood glucose levels) (Wilding 2012, *Annals of Internal Medicine*, 20 March 2012).
- 7.8 With regard to HbA1c improvement demonstrated in Wilding, the PBAC noted that patients on dapagliflozin 10mg achieved a change in HbA1c of -0.57% (-0.72%, -0.42%) compared with placebo. The PBAC also noted that patients on dapagliflozin achieved a change in body weight of -2.04 (-2.59, -1.48) compared with an increase of 0.43kg on placebo.
- 7.9 With regard to the adjusted mean change from baseline in daily insulin dose in Wilding, the PBAC noted a reduction of 1.18 IU at 24 weeks in the dapagliflozin 10mg group, compared with an increase of 5.65 in the placebo group. At 48 weeks, the mean change was a reduction of 0.70 IU for dapagliflozin compared with an increase of 10.54 IU for placebo. The PBAC considered that the absolute and relative decreases in insulin dose, although small, were relevant.
- 7.10 The PBAC noted the sponsor's assertion that sitagliptin does not result in an increased mean daily insulin dose. In support of this position the sponsor offered the following arguments:
- There was no significant increase in insulin dose between the sitagliptin and placebo arm of P051;
 - The insulin dose changes in P051 and Wilding were comparable;
 - P260 is a treat-to-target trial with a forced insulin titration schedule;
 - Patients in both study arms were required to increase their insulin dose to reach a set glycaemic target;
 - In P260, patients in the sitagliptin + insulin titration arm had significantly better glycaemic control than patients in the insulin up-titration only arm;
 - Patients in the sitagliptin arm used less insulin, not more, than patients in the placebo arm and experienced significantly less hypoglycaemia and less weight gain;
 - The reduction in HbA1c in the sitagliptin arm of P260 was significantly better than the sitagliptin arm of P051 or the dapagliflozin arm of Wilding.
- 7.11 The PBAC made the following observations on the sponsor's arguments:
- Increases in insulin dose in P051 were not permitted by the trial design, therefore a claim of no significant dose increase was not valid;

- A mean increase from baseline of 19 IU in daily insulin dose for the sitagliptin arm of P260 could not reasonably be interpreted as using “less insulin”, particularly as the comparator, dapagliflozin, demonstrated absolute and relative decreases in daily insulin dose;
 - The trial data from P051 and P260 were inconsistent with regard to the incidence of hypoglycaemia and weight gain, therefore it was not possible to conclude that the incidence of these adverse events would be lower with sitagliptin compared with placebo;
 - The comparison of LS mean change in HbA1c across P260, P051 and Wilding showed that the reduction in the sitagliptin arm of P260 was lower than both the sitagliptin arm of P051 and the dapagliflozin arm of Wilding.
- 7.12 The PBAC recalled its July 2015 conclusion that the clinical data presented were not adequate to support a claim of non-inferior comparative effectiveness (as measured by reduction in HbA1c) and similar reduction in mean daily insulin dose for sitagliptin compared to dapagliflozin.
- 7.13 With regard to the effect of sitagliptin on HbA1c, the PBAC considered that sitagliptin is effective in reducing HbA1c in combination with insulin. The PBAC noted the limitations on the available data, however concluded that sitagliptin is likely to be non-inferior to dapagliflozin in this regard.
- 7.14 The PBAC reiterated its view that the increased daily insulin dose accompanying sitagliptin treatment should be taken into account in the cost-minimisation analysis of any future resubmission.
- 7.15 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.