

7.10 VILDAGLIPTIN, 50mg tablet, VILDAGLIPTIN AND METFORMIN, 50mg/500mg, 50mg/850mg, 50mg/1000mg tablet, Galvus®, Galvumet® Novartis Pharmaceuticals Australia Pty Ltd.


1 Purpose of Application

1.1 To request Authority Required (Streamlined) listing for vildagliptin for treatment of type 2 diabetes as part of triple combination therapy with metformin and a sulfonylurea when combination therapy with both agents does not provide adequate glycaemic control.

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.

2.2 Prices for the requested listing have been adjusted to incorporate the 5% statutory price reduction for vildagliptin to be implemented in April 2016.

| Name, Restriction, Manner of administration and form | Max. Qty | No. of Rpts | Dispensed Price for Max. Qty | Proprietary Name and Manufacturer |
|--|----------|-------------|---|-----------------------------------|
| VILDAGLIPTIN Tablet 50mg | 60 | 5 |  | Galvus® Novartis |

| | |
|------------------------------------|--|
| Category / Program | GENERAL – General Schedule (Code 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 |
| Treatment phase: | N/A |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> 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>Patients 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) despite treatment with maximally tolerated doses of metformin and a sulfonylurea <i>optimal doses of dual oral therapy</i>; OR</p> <p>Patients must have, or have had, where HbA1c measurement is clinically appropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 weeks period prior to initiation with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor despite treatment with maximally tolerated doses of metformin and a sulfonylurea <i>optimal doses of dual oral therapy</i>.</p> |
| <p>Prescriber Instructions</p> | <p>The date and level of the qualifying HbA1c must be, or must have been, documented in the patient's medical records at the time treatment with a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), a glucagon-like peptide-1 or a sodium-glucose co-transporter 2 (SGLT2) 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 n SGLT2 inhibitor was initiated.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:</p> <ul style="list-style-type: none"> (a) clinical conditions with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or (b) had red cell transfusion within the previous 3 months. <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 document 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> |

Public Summary Document – March 2016 PBAC Meeting

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| Administrative Advice | <p><u>Continuing Therapy Only:</u> 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. Further information can be found in the Explanatory Notes for Nurse Practitioners.</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> <p><i>PBS subsidised dual oral therapy does not include concomitant use of two of either: a gliptin, a glitazone or an SGLT2 inhibitor.</i></p> |
|------------------------------|---|

| Name, Restriction, Manner of administration and form | Max. Qty | №.of Rpts | Dispensed Price for Max. Qty | Proprietary Name and Manufacturer |
|--|----------|-----------|------------------------------|-----------------------------------|
| VILDAGLIPTIN/METFORMIN | | | | |
| Tablet 50mg/500mg | 60 | 5 | F | Galvumet® Novartis |
| Tablet 50mg/850mg | 60 | 5 | | |
| Tablet 50mg/1000mg | 60 | 5 | | |

| | |
|------------------------------------|---|
| Category / Program | GENERAL – General Schedule (Code 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 |
| Treatment phase: | N/A |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined |
| Clinical criteria: | <p>The treatment must be in combination with a sulfonylurea,</p> <p>AND</p> <p>Patients 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) despite treatment with maximally tolerated doses of metformin and a sulfonylurea <i>optimal doses of dual oral therapy;</i></p> <p>OR</p> <p>Patients 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 weeks period prior to initiation with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor despite treatment with maximally tolerated doses of metformin and a sulfonylurea <i>optimal doses of dual oral therapy.</i></p> |

| | |
|---------------------------------------|--|
| <p>Prescriber Instructions</p> | <p>The date and level of the qualifying HbA1c must be, or must have been, documented in the patient's medical records at the time treatment with a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), a glucagon-like peptide-1 or a sodium-glucose co-transporter 2 (SGLT2) 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 n 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 style="padding-left: 40px;">(a) clinical conditions with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or</p> <p style="padding-left: 40px;">(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 document 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 <i>fixed dose combination</i>.</p> |
| <p>Administrative Advice</p> | <p><u>Continuing Therapy Only:</u> <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. Further information can be found in the Explanatory Notes for Nurse Practitioners.</i></p> <p>This drug <i>fixed dose combination tablet</i> is not PBS-subsidised for use as <i>initial therapy</i> or in combination with a thiazolidinedione (glitazone), a glucagon-like peptide-1 or an SGLT2-inhibitor</p> <p><i>PBS subsidised dual oral therapy does not include concomitant use of two of either: a gliptin, a glitazone or an SGLT2 inhibitor.</i></p> |

- 2.3 The submission stated the listing was requested on a cost minimisation-basis compared to dapagliflozin, but the submission requested the same price for vildagliptin and vildagliptin/metformin fixed dose combinations (FDCs) as for their current dual oral therapy listings. The submission assumed that cost-offsets already applied in the PBS dual therapy listing would apply to the listing of vildagliptin and dapagliflozin when used in triple oral therapy.

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

3 Background

- 3.1 TGA status at time of PBAC consideration: Vildagliptin was registered by the TGA on 27 August 2013 for treatment in triple combination with a sulfonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control. Vildagliptin/metformin FDC was registered by the TGA on 12 June 2013 for use in combination with a sulfonylurea (i.e. triple combination therapy) as an

adjunct to diet and exercise in patients inadequately controlled with metformin and a sulfonylurea.

- 3.2 Vildagliptin (with metformin or a sulfonylurea) and vildagliptin/metformin FDC are currently PBS listed for dual oral combination therapy for type 2 diabetes.
- 3.3 Vildagliptin and vildagliptin/metformin FDC were previously considered by the PBAC in July 2013 as concurrent submissions for triple therapy in type 2 diabetes. The submissions were rejected, as the PBAC did not accept pioglitazone as the appropriate comparator, in view of concerns about adverse cardiovascular events and its diminishing use in the clinical treatment algorithm for type 2 diabetes. The secondary comparators exenatide and linagliptin were also not accepted as appropriate comparators.
- 3.4 The PBAC considered a submission for triple oral therapy for linagliptin at the March 2016 PBAC meeting [refers item 7.05].

4 Clinical place for the proposed therapy

- 4.1 Type 2 diabetes as triple oral therapy in combination with metformin and a sulfonylurea when therapy with both agents does not provide adequate glycaemic control. Alternative agents for triple therapy (with metformin and a sulfonylurea) include oral therapies pioglitazone, dapagliflozin and other DPP-4 inhibitors or injection therapies insulin and exenatide.

5 Comparator

- 5.1 Dapagliflozin, with sitagliptin and saxagliptin as supplementary comparators. These were appropriate comparators. Dapagliflozin was the nominated main comparator as it was the only appropriate comparator with a PBS-listing for triple oral therapy at the time of the submission. Dapagliflozin/metformin XR FDC, sitagliptin and saxagliptin and their associated FDCs were subsequently PBS-listed for triple oral therapy (1 December 2015).

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

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

Clinical trials

- 6.7 The submission was based on an indirect comparison of one vildagliptin trial (Trial 23152) with placebo + metformin + sulfonylurea as common comparator, with:
- One dapagliflozin trial (Matthaei 2015)
 - Three sitagliptin trials (Hermansen 2007, NCT01076075, NCT01590771)
 - One saxagliptin trial (Moses 2014)

The submission also presented the results of a head-to-head study of vildagliptin and saxagliptin (Chen 2015) as supplementary evidence, as the study was open label and limited information was available from the published abstract.

- 6.8 Details of the trials presented in the submission are provided in the table below.

Table 1: Trials and associated reports presented in the submission

| Trial | Protocol title/Publication title | Publication citation |
|--|---|---|
| Common reference placebo + metformin + sulfonylurea | | |
| <i>Vildagliptin</i> | | |
| Trial 23152 | A multi-centre, randomised, double-blind, placebo controlled study to evaluate the efficacy and safety of 24 weeks treatment with vildagliptin 50mg bid as add-on therapy to metformin plus glimepiride in patients with type 2 diabetes. | Clinical Study Report, 2 Feb 2012 |
| | Lukashevich V, et al. Efficacy and safety of vildagliptin in patients with type 2 diabetes mellitus inadequately controlled with dual combination of metformin and sulphonylurea. | Diabetes, Obesity and Metabolism 2014, 16:403-409. |
| | Lukashevich V, et al. Vildagliptin efficacy and safety in patients with type 2 diabetes inadequately controlled on dual metformin plus sulfonylurea therapy. | Diabetologia 2012, 55(Suppl. 1):S353, abstract 856. |
| <i>Dapagliflozin</i> | | |
| Matthaei 2015 | Matthaei S, Bowering K, Rohwedder K, et al. Dapagliflozin improves glycaemic control and reduces body weight as add-on therapy to metformin plus sulfonylurea: a 24-week randomized, double-blind clinical trial. | Diabetes care 2015, 38(3):365-372. |
| | Matthaei S, et al. Improvement in glycaemic control and reduction in body weight over 52 weeks with dapagliflozin as add-on therapy to metformin plus sulphonylurea. (abstract only) | Diabetologia, 2014, 57(1): S347. |
| | Sternhufvud C, et al. Change in quality of life (EQ-5D) among type 2 diabetes mellitus patients inadequately controlled with metformin plus sulfonylurea and treated with dapagliflozin as triple therapy regimen for 24 weeks. (abstract only) | Value in Health 2014, 17(3): A257 |
| | Matthaei S, et al. Efficacy and safety of dapagliflozin in patients with T2DM inadequately controlled on metformin plus sulfonylureas according to background sulfonylurea. (abstract only) | Diabetes 2015, 64: A332 |
| | Matthaei S, et al. Dapagliflozin improves glycaemic control and reduces body weight as add-on therapy to metformin plus sulphonylurea. (abstract only) | Diabetologia 2013, 56: S374-S375 |
| <i>Sitagliptin</i> | | |

| Trial | Protocol title/Publication title | Publication citation |
|------------------------------------|--|---|
| NCT01076075 | A study to evaluate the safety and efficacy of sitagliptin 100mg in participants with type 2 diabetes mellitus who have inadequate glycaemic control (MK-0431-229) | Clinicaltrials.gov reference NCT01076075 |
| NCT01590771 | A study in China evaluating the safety and efficacy of adding sitagliptin to stable therapy with sulfonylurea with or without metformin in participants with Type 2 diabetes mellitus (MK-0431-253) (clinicaltrials.gov) | Clinicaltrials.gov reference NCT01590771 |
| Hermansen 2007 | Hermansen K, Kipnes M, Luo E, et al. 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. | Diabetes, Obesity and Metabolism 2007, 9: 733-745. |
| Saxagliptin | | |
| Moses 2014 | Moses RG, Kalra S, Brook D, et al. A randomized controlled trial of the efficacy and safety of saxagliptin as add-on therapy in patients with type 2 diabetes and inadequate glycaemic control on metformin plus a sulphonylurea. Moses et al. Saxagliptin (SAXA) effectively reduces HbA1c and is well tolerated when added to a combination of metformin (MET) and sulfonylurea (SU). (abstract only) | Diabetes, Obesity and Metabolism 2014, 16: 443-450. Diabetes 2012, 61, A282. |
| Vildagliptin vs saxagliptin | | |
| Chen 2015 | Chen X, Wang J, Huang X, et al. Effects of vildagliptin vs saxagliptin on daily acute glucose fluctuation in Chinese type 2 diabetics inadequately controlled with dual combination of metformin and sulphonylurea (abstract only). | Diabetes, 64, A318 |

Abbreviations: RCT, randomised controlled trial

Source: Table 8, pp24-26 of the submission.

- 6.9 The key features of the randomised trials are summarised in the table below. There were some differences in baseline characteristics within and between trials. There were more men in the placebo than the dapagliflozin arm of Matthaehi 2015, and the study population was predominantly Asian in the vildagliptin trial 23152, and saxagliptin trial Moses 2014. Both Chen 2015 and sitagliptin trial NCT01590771 included only Chinese patients. It was unclear whether the differences in the ethnicity of patients in the trial would affect the applicability of results to the requested PBS population.

Table 2: Key features of the included evidence

| Trial | N | Design/ duration | Risk of bias | Patient population | Outcome(s) |
|--|-----|-----------------------------|--------------|--|----------------------------------|
| Vildagliptin 100mg vs placebo, in combination with metformin and a sulfonylurea | | | | | |
| Trial 23152 | 318 | R, DB, MC, PG, PC, 24 weeks | Low | Aged ≥18 - ≤80 years with T2DM; HbA1c ≥7.5% - ≤11% | HbA1c, responders, FPG |
| Dapagliflozin 10mg vs placebo, in combination with metformin and a sulfonylurea | | | | | |
| Matthaehi 2015 | 218 | R, DB, MC, PG, PC, 24 weeks | Low | Aged ≥18 with T2DM; HbA1c ≥7.0% - ≤10.5% | HbA1c, responders, FPG, SBP |
| Sitagliptin 100mg vs placebo, in combination with metformin and a sulfonylurea | | | | | |
| Hermansen 2007 (Stratum 2) ^a | 229 | R, DB, MC, PG, PC, 24 weeks | Low | Aged ≥18 - ≤75 years with T2DM; HbA1c ≥7.5% - ≤10.5% | HbA1c, responders, plasma lipids |
| NCT01076075 | 427 | R, DB, MC, PG, PC, 24 weeks | Low | Aged ≥18 - ≤78 years with T2DM; HbA1c ≥7.5% - ≤10.5% | HbA1c, FPG, 2hr PMG |
| NCT01590771 ^b | 498 | R, DB, MC, PG, PC, | Low | Chinese patients aged | HbA1c, FPG, 2hr PMG |

| | | | | | |
|--|-----|--|------|--|---------------------------------|
| | | 24 weeks | | ≥18 - ≤80 years with T2DM; HbA1c ≥7.5% - ≤11% | |
| Pooled trials | 419 | Assessed change from baseline in HbA1c at 24 weeks | | | |
| Saxagliptin 5mg vs placebo, in combination with metformin and a sulfonylurea | | | | | |
| Moses 2014 | 257 | R, DB, MC, PG, PC, 24 weeks | Low | Aged ≥18 with T2DM; HbA1c ≥7.0% - ≤10.0% | HbA1c, responders, FPG, 2hr PMG |
| Vildagliptin 100mg vs saxagliptin 5mg, in combination with metformin and a sulfonylurea | | | | | |
| Chen 2015 | 73 | R, OL, 24 weeks | High | Chinese patients with T2DM; mean age 63±6.6yrs; mean HbA1c 8.35±0.7% | MAGE, HbA1c, FPG, 2hr PMG |

^a Stratum 2 patients were taking a combination of metformin + sulfonylurea (Stratum 1 patients were taking metformin only)

^b Trial included arms where patients could take a sulfonylurea with and without added metformin. The limited results available for this study show that the sitagliptin arm with MET+SU included between 109 and 113 patients, while the placebo arm with MET+SU included between 111 and 114 patients in the analysis of outcomes.

Abbreviations: DB, double blind; FPG, fasting plasma glucose; HbA1c, glycosylated haemoglobin; MAGE, mean amplitude of glycaemic excursions; MC, multi-centre; OL, open label; PC, placebo controlled; PG, parallel group; PMG, post meal glucose; R, randomised; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.

Source: compiled during the evaluation

Comparative effectiveness

- 6.10 The results of the indirect comparison for the key outcome, mean change from baseline in HbA1c at 24 weeks are shown in Table 3. The heterogeneity of the pooled sitagliptin trial results means that the indirect comparison of these trials with vildagliptin should be interpreted with caution.

Table 3: Mean change in HbA1c from baseline to week 24

| Trial ID | Mean change HbA1c% baseline to week 24 (95% CI) | | | Mean difference (95% CI) | Indirect RD (95% CI) |
|---|---|----------------------|----------------------|--------------------------|----------------------|
| | Vildagliptin | Placebo | Comparator | | |
| Vildagliptin 100mg vs dapagliflozin 10mg | | | | | |
| Trial 23152 | -1.01 (-1.19, -0.83) | -0.25 (-0.43, -0.07) | - | -0.76 (-0.98, -0.53) | -0.070 |
| Matthaei 2015 | - | -0.17 (-0.31, -0.02) | -0.86 (-1.00, -0.72) | -0.69 (-0.89, -0.49) | (-0.39, 0.25) |
| Vildagliptin 100mg vs sitagliptin 100mg | | | | | |
| Trial 23152 | -1.01 (-1.19, -0.83) | -0.25 (-0.43, -0.07) | - | -0.76 (-0.98, -0.53) | -0.100 |
| Sitagliptin ^a | - | - | - | -0.66 (-0.92, -0.40) | (-0.46, 0.26) |
| Vildagliptin 100mg vs saxagliptin 5mg | | | | | |
| Trial 23152 | -1.01 (-1.19, -0.83) | -0.25 (-0.43, -0.07) | - | -0.76 (-0.98, -0.53) | -0.100 |
| Moses 2014 | - | -0.08 (-0.23, 0.07) | -0.74 (-0.89, -0.60) | -0.66 (-0.89, -0.45) | (-0.43, 0.23) |

^a Pooled sitagliptin trials: Hermansen 2007, NCT01076075 and NCT0159077

Abbreviations: CI, confidence interval; RD, risk difference

Source: Table 25, p53; Table 26, p55 of the submission

- 6.11 The results of the indirect analyses were consistent with no statistically significant differences between vildagliptin and dapagliflozin, sitagliptin or saxagliptin, in combination with metformin and a sulfonylurea, in reduction in HbA1c at 24 weeks. The observed differences were within the minimal clinically important difference of 0.4% specified in the submission, and previously accepted by the PBAC (Dapagliflozin, March 2015 Public Summary Document). Similar results were reported for the proportion of HbA1c responders at 24 weeks.

- 6.12 No studies were identified that investigated the use of vildagliptin/metformin FDC in triple therapy. The submission re-presented evidence supporting the bioequivalence of the vildagliptin/metformin FDCs, and vildagliptin and metformin given separately. The three bioequivalence studies presented were the basis of the recommendation to list vildagliptin/metformin FDC for dual therapy at the November 2010 PBAC meeting.

Comparative harms

- 6.13 In vildagliptin Trial 23152, there were no differences in the percentage of serious or clinically significant adverse events in the vildagliptin and placebo arms. One patient in the placebo group died due to suicide. No clinically significant hepatic adverse events were reported. Reported rates of hypoglycaemia were low (5.1% in the vildagliptin arm and 1.9% in the placebo arm).
- 6.14 An indirect comparison of key adverse events reported in the trials is provided in Table 4. There were no significant differences in the overall rate of adverse events or hypoglycaemic events between vildagliptin and all comparators. However, the potential differences in definitions of adverse events and wide confidence intervals suggest the results based on indirect comparisons should be interpreted with caution.

Table 4: Indirect comparisons of key adverse events in the randomised trials

| Trial (all 24 weeks duration, comparison with vildagliptin Trial 23152) | Odds Ratio (95% CI) |
|--|---------------------|
| At least one adverse event | |
| Vildagliptin 100mg vs dapagliflozin 10mg (Matthaei 2015) | 0.72 (0.36, 1.44) |
| Vildagliptin 100mg vs sitagliptin 100mg (pooled studies) | 0.96 (0.53, 1.74) |
| Vildagliptin 100mg vs saxagliptin 5mg (Moses 2014) | 1.62 (0.82, 3.21) |
| One or more episodes of hypoglycaemia | |
| Vildagliptin 100mg vs dapagliflozin 10mg (Matthaei 2015) | 0.73 (0.12, 4.25) |
| Vildagliptin 100mg vs sitagliptin 100mg (Hermansen 2007, stratum 2 only) | 0.13 (0.01, 1.46) |
| Vildagliptin 100mg vs saxagliptin 5mg (Moses 2014) | 1.67 (0.33, 8.54) |

Source: Table 34, p68; Table 36, p70 of the submission

Abbreviations: CI, confidence interval; MET, metformin; SD, standard deviation; SU, sulfonylurea.

Clinical claim

- 6.15 The submission described vildagliptin as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety compared with dapagliflozin, sitagliptin and saxagliptin when used in triple therapy with metformin and a sulfonylurea. This claim was adequately supported:
- Vildagliptin produces comparable reductions in HbA1c to dapagliflozin, sitagliptin and saxagliptin, when used in combination with metformin and a sulfonylurea in type 2 diabetes;
 - Rates of adverse events, serious adverse events and hypoglycaemia events were similar between vildagliptin and dapagliflozin, sitagliptin and saxagliptin. However, the potential differences in definitions of adverse events and wide confidence intervals suggest the results based on indirect comparisons should be interpreted with caution. The ESC considered that this clinical claim was adequately supported.

- 6.16 The submission also re-iterated the claim that vildagliptin/metformin FDC is equivalent to the two components given separately. This claim has been previously accepted by the PBAC (November 2010 PBAC meeting).
- 6.17 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 6.18 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

- 6.19 Equi-effective doses were based on the trial-based indirect comparison of vildagliptin and dapagliflozin, both in combination with metformin and a sulfonylurea, with placebo as common comparator:
- Vildagliptin 100mg/day (given as two 50mg doses) is equivalent to dapagliflozin 10mg/day. The ESC considered this appropriate.
- 6.20 Therapeutic Relativity sheets from 1 December 2015 state the following equi-effective doses for dual oral therapy:
- Vildagliptin 100mg/day (given as two 50mg doses) is equivalent to sitagliptin 100mg/day (when taken in combination with metformin)
 - Vildagliptin 50mg/day is equivalent to sitagliptin 100mg/day (when taken in combination with a sulfonylurea)
 - Saxagliptin 5mg/day is equivalent to sitagliptin 100mg/day
 - Dapagliflozin 10mg/day is equivalent to sitagliptin 100mg/day.
- 6.21 The submission did not present a cost-minimisation analysis, rather a comparison of the proposed price of vildagliptin with the current price of dapagliflozin in triple oral therapy. The proposed prices for vildagliptin were the same as the currently PBS-listed prices for vildagliptin and vildagliptin/metformin FDC. During the evaluation, the prices for vildagliptin and sitagliptin (and associated FDCs) were adjusted to incorporate the 5% statutory price reduction to be implemented in April 2016.
- 6.22 The submission stated that the current price for vildagliptin already takes into account the cost of liver function tests to be conducted every three months in the first year and periodically thereafter. At the November 2010 meeting, the PBAC recommended listing of vildagliptin 100mg/day for dual oral therapy on a cost-minimisation basis with sitagliptin 100mg/day. However, in dual therapy with a sulfonylurea, the recommended dose for vildagliptin is 50mg/day. The PBAC considered that the additional costs associated with liver function tests required for patients receiving vildagliptin were offset by the lower dose and subsequent cost of vildagliptin per day compared to sitagliptin per day when either agent was used in combination with a sulfonylurea, when at least 40% of vildagliptin was used in combination with a sulfonylurea (March 2010 Public Summary Document). In the case of triple oral therapy, the recommended dose of vildagliptin is 100mg/day (given as 2 x 50mg doses). The PBAC may wish to consider whether the current PBS-listed price for vildagliptin is appropriate for triple therapy, as the cost of liver function testing is no longer offset by a proportion of use at a lower dosage.

- 6.23 The ESC noted that the submission argued that 50% of patients under the proposed triple oral therapy listing would have previously received treatment under the dual oral therapy listing, and thus not require a liver function test every three months in the first year. The ESC further noted that if all patients receiving vildagliptin as part of a triple oral therapy regimen required liver function testing in the first year of treatment, this could turn the projected PBS savings into an overall cost to the PBS. The Pre-PBAC Response (p. 2) argued that the likelihood of all vildagliptin triple therapy patients being naïve to this molecule prior to being prescribed triple therapy is very low. The PBAC considered this reasonable, and noted that in practice many patients with type 2 diabetes mellitus may receive annual LFTs regardless of therapy prescribed.

Drug cost/patient/year: \$717.30

- 6.24 \$717.30 for vildagliptin 50mg \$58.94x 30 day supply (60 tablets) x 12.17 scripts per year); up to \$725.33 for vildagliptin/metformin FDC 50mg/1000mg; compared with \$751.10 for dapagliflozin 10mg (\$57.60 x 28 day supply (56 tablets) x 13.04 scripts per year); and up to \$793.48 for dapagliflozin/metformin XR FDC 5mg/1000mg (DPMQ). The price of dapagliflozin includes a cost-offset for monitoring and treatment of genital mycotic infections and urinary tract infections.

Estimated PBS usage & financial implications

- 6.25 This submission was not considered by DUSC. A market share approach was used. Medicare services data from 2014-2015 for overall use of vildagliptin, dapagliflozin, sitagliptin and saxagliptin were used to predict overall market growth in the absence of any triple therapy PBS listings for these agents. The 10% Medicare sample was used to determine the proportion of overall use by patients as triple oral therapy (use outside of PBS restrictions). The submission then projected utilisation estimates in scenarios where dapagliflozin, sitagliptin and saxagliptin had triple therapy PBS listings, and then where vildagliptin also had a triple therapy PBS listing. Incremental growth in vildagliptin scripts between the two scenarios was the basis for the submission's financial estimates. Costs were calculated using weighted average DPMQs for the individual medicines and their fixed dose combinations. Costs were adjusted during the evaluation to account for the 5% statutory price reductions for vildagliptin and sitagliptin on 1 April 2016.

Table 5: Estimated use and financial implications

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|--|-----------|-----------|------------|------------|------------|
| Overall vildagliptin, dapagliflozin, sitagliptin and saxagliptin market in absence of triple therapy listings | | | | | |
| Total scripts ^a | | | | | |
| Total patients ^b | | | | | |
| Triple therapy patients (20% of total) | | | | | |
| - Vildagliptin | | | | | |
| - Comparators | | | | | |
| Non-triple therapy patients | | | | | |
| Market with triple therapy listings for dapagliflozin, sitagliptin and saxagliptin (but not vildagliptin) | | | | | |
| New patients switching from other therapies (% of all patients) | 3% | 4% | 5% | 6% | 7% |
| New patients 'upgrading' from dual oral therapy (% non-triple therapy) | 6% | 7% | 8% | 9% | 10% |
| Total triple therapy patients (new plus existing) | | | | | |
| - Vildagliptin (% of total vildagliptin patients) | 16% | 15% | 14% | 13% | 12% |
| - Comparators (patients) | | | | | |
| Market with triple therapy listings for dapagliflozin, sitagliptin and saxagliptin AND vildagliptin | | | | | |
| Total triple therapy market (patients) | | | | | |
| - Vildagliptin (% of triple therapy patients) | 10% | 11% | 12% | 13% | 14% |
| - Comparators (patients) | | | | | |
| Incremental vildagliptin patients / scripts due to PBS listing for vildagliptin | | | | | |
| Incremental vildagliptin patients | | | | | |
| Incremental vildagliptin scripts | | | | | |
| Reduction in comparator scripts | | | | | |
| Reduction in dapagliflozin, sitagliptin, saxagliptin patients | | | | | |
| Reduction in dapagliflozin, sitagliptin, saxagliptin scripts | | | | | |
| Net cost to PBS/RPBS/MBS | | | | | |
| Net cost to PBS/RPBS | -\$ | -\$ | -\$ | -\$ | -\$ |
| Net cost to MBS ^c | \$ | \$ | \$ | \$ | \$ |
| Net cost to PBS/RPBS/MBS | \$ | \$ | -\$ | -\$ | -\$ |

^a Total scripts were estimated based on assumed growth from 2014-2015 for dapagliflozin, saxagliptin, saxagliptin/metformin XR FDC, sitagliptin, sitagliptin/metformin FDC, sitagliptin/metformin XR FDC, vildagliptin and vildagliptin/metformin FDC

^b Assuming 12.17 scripts per year for vildagliptin and 13.04 scripts per year for the comparators as estimated in the submission

^c Costs to MBS were for liver function testing and associated GP consultations; submission assumed 50% of new patients each year were vildagliptin-naïve and would require more intensive liver function testing in the first year of use.

Abbreviations: DPP-4, dipeptidyl peptidase-4; FDC, fixed dose combination; SGLT-2, sodium-glucose co-transporter-2

Source: Excel workbook: Att 6 Section E spreadsheets.xls

The redacted table shows that at year 5, the estimated number of vildagliptin (triple therapy) patients was less than 10,000, and the net save to the PBS would be less than \$10 million.

- 6.26 Whether the estimated costs are an under- or over-estimate is unknown due to the number of assumptions used in calculating utilisation of vildagliptin. There are difficulties in predicting a market for vildagliptin triple therapy when there are no current utilisation data for the new triple therapy PBS listings for the comparators due to their recent addition to the PBS, and there is an existing market for triple therapy where use was outside of PBS restrictions.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required (streamlined) listing of vildagliptin in triple oral combination with metformin and a sulfonylurea on a cost minimisation basis with dapagliflozin. The equi-effective doses were vildagliptin 100mg/day (given as two 50mg doses) and dapagliflozin 10mg/day.
- 7.2 The PBAC recommended the Authority Required (Streamlined) listing of vildagliptin with metformin (FDC) in combination with a sulfonylurea on a cost minimisation basis to the individual components taken concomitantly.
- 7.3 The PBAC accepted that dapagliflozin was an appropriate comparator. The PBAC also considered that sitagliptin and saxagliptin were also appropriate secondary comparators.
- 7.4 The PBAC considered that the clinical claim of non-inferior comparative effectiveness and safety between vildagliptin and dapagliflozin, sitagliptin and saxagliptin when used in triple oral therapy with metformin and a sulfonylurea, was reasonable.
- 7.5 The PBAC recalled from previous consideration of treatments for diabetes that the PBS market for these drugs is not yet stable. The PBAC considered that it was not possible to exclude the possibility that the market would not grow further upon the PBS listing of vildagliptin and vildagliptin with metformin for triple oral therapy. .
- 7.6 The PBAC recalled its previous advice that the additional costs associated with liver function tests (LFTs) required for patients receiving vildagliptin were offset by the lower dose and subsequent cost of vildagliptin per day compared to sitagliptin per day when either agent was used in combination with a sulfonylurea, when at least 40% of vildagliptin was used in combination with a sulfonylurea (March 2010 Public Summary Document). The PBAC noted that in the case of triple oral therapy, the recommended dose of vildagliptin is 100mg/day (given as 2 x 50mg doses), and it could therefore be considered the cost of LFTs is no longer offset by a proportion of use at a lower dosage. However, the PBAC noted that the submission had factored in these costs by assuming that 50% of patients under the proposed triple oral therapy listing would have previously received treatment under the dual oral therapy listing, and thus not require a LFT every three months in the first year (see Table 5). The PBAC noted the ESC advice that if all patients receiving vildagliptin as part of a triple oral therapy regimen required liver function testing in the first year of treatment, this could turn the projected PBS savings into an overall cost to the PBS. The Pre-PBAC Response (p. 2) argued that the likelihood of all vildagliptin triple therapy patients being naïve to this molecule prior to being prescribed triple therapy is very low. The PBAC considered this reasonable, and noted that in practice many patients with type 2 diabetes mellitus may receive annual LFTs regardless of therapy prescribed.
- 7.7 The PBAC recommended that the restriction wording for these listings be consistent with the restrictions for triple oral therapy listings for sitagliptin and its FDC, which are

in turn consistent with the SGLT2 inhibitor restrictions.

- 7.8 The PBAC recalled from previous analyses by DUSC and the Post Market Review of Diabetes Drugs that the PBS market for treatments for diabetes is not yet stable. The PBAC considered that it was not possible to exclude the possibility that the market would not grow further upon the PBS listing vildagliptin and vildagliptin with metformin for triple oral therapy.
- 7.9 The PBAC advised that vildagliptin and vildagliptin with metformin FDC are suitable for prescribing by Nurse Practitioners for Continuing Therapy Only.
- 7.10 Under Section 101(3BA) of the *National Health Act 1953*, the PBAC advised that vildagliptin should be treated as interchangeable on an individual patient basis with sitagliptin and saxagliptin for triple oral therapy. The PBAC advised that vildagliptin with metformin should be treated as interchangeable on an individual patient basis with: sitagliptin with metformin and saxagliptin with metformin for triple oral therapy.
- 7.11 The PBAC considered that there was no reason to exempt vildagliptin and vildagliptin with metformin FDC from the Early Supply Rule.

Outcome:

Recommended

8 Recommended listing

8.1 Amend existing/recommended listing as follows:

| Name, Restriction, Manner of administration and form | Max. Qty | No. of Rpts | Proprietary Name and Manufacturer | |
|---|-------------|----------------|-----------------------------------|----------|
| VILDAGLIPTIN Tablet 50mg | 60 | 5 | Galvus® | Novartis |

| | |
|------------------------------------|--|
| Category / Program | GENERAL – General Schedule (Code 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 |
| Treatment phase: | N/A |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined |

Public Summary Document – March 2016 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>Patients 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) despite treatment with optimal doses of dual oral therapy; OR</p> <p>Patients must have, or have had, where HbA1c measurement is clinically appropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 weeks period prior to initiation with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor despite treatment with optimal doses of dual oral therapy.</p> |
| <p>Prescriber Instructions</p> | <p>The date and level of the qualifying HbA1c must be, or must have been, documented in the patient's medical records at the time treatment with a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), a glucagon-like peptide-1 or a sodium-glucose co-transporter 2 (SGLT2) 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 n SGLT2 inhibitor was initiated.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:</p> <ul style="list-style-type: none"> (a) clinical conditions with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or (b) had red cell transfusion within the previous 3 months. <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 document 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><u>Continuing Therapy Only:</u> 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. Further information can be found in the Explanatory Notes for Nurse Practitioners.</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> <p>PBS subsidised dual oral therapy does not include concomitant use of two of either: a gliptin, a glitazone or an SGLT2 inhibitor.</p> |

Public Summary Document – March 2016 PBAC Meeting

| Name, Restriction, Manner of administration and form | Max. Qty | №.of Rpts | Proprietary Name and Manufacturer | |
|---|-------------|--------------|-----------------------------------|----------|
| VILDAGLIPTIN/METFORMIN | | | | |
| Tablet 50mg/500mg | 60 | 5 | Galvumet® | Novartis |
| Tablet 50mg/850mg | 60 | 5 | | |
| Tablet 50mg/1000mg | 60 | 5 | | |

| | |
|------------------------------------|--|
| Category / Program | GENERAL – General Schedule (Code 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 |
| Treatment phase: | N/A |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined |
| Clinical criteria: | <p>The treatment must be in combination with a sulfonylurea,</p> <p>AND</p> <p>Patients 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) despite treatment with optimal doses of dual oral therapy;</p> <p>OR</p> <p>Patients 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 weeks period prior to initiation with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor despite treatment with optimal doses of dual oral therapy.</p> |

| | |
|---------------------------------------|---|
| <p>Prescriber Instructions</p> | <p>The date and level of the qualifying HbA1c must be, or must have been, documented in the patient's medical records at the time treatment with a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), a glucagon-like peptide-1 or a sodium-glucose co-transporter 2 (SGLT2) 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 n 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 style="padding-left: 40px;">(a) clinical conditions with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or</p> <p style="padding-left: 40px;">(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 document 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><u>Continuing Therapy Only:</u> 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. Further information can be found in the Explanatory Notes for Nurse Practitioners.</p> <p>This fixed dose combination is not PBS-subsidised for use as initial therapy or in combination with a thiazolidinedione (glitazone), a glucagon-like peptide-1 or an SGLT2-inhibitor</p> <p>PBS subsidised dual oral therapy does not include concomitant use of two of either: a gliptin, a glitazone 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.