PUBLIC SUMMARY DOCUMENT
Product: Sitagliptin with Simvastatin, tablets, 100 mg–10 mg, 100 mg–20 mg and 100 mg–40 mg, Juvicor®
Sponsor: Merck Sharp & Dohme (Australia) Pty Ltd
Date of PBAC Consideration: November 2012

1. Purpose of Application

The submission sought an Authority Required (Streamlined) listing for use in patients with type 2 diabetes who are currently receiving treatment with simvastatin and who satisfy the criteria for prescribing dipeptidyl peptidase 4 (DPP-4) inhibitors ('gliptins').

This application was considered under the TGA/PBAC parallel process. The Clinical Evaluation Report and the Delegate's overview were received during the evaluation, and both supported the registration of the sitagliptin/simvastatin fixed dose combination.

2. Background

Simvastatin

Simvastatin was first listed on the PBS on 1 December 1990.

Sitagliptin

In March 2008, the PBAC recommended an Authority required listing of sitagliptin for the treatment, as part of dual oral combination therapy with metformin or a sulfonylurea, of a patient with Type 2 diabetes whose HbA1c is greater than 7% prior to initiation of sitagliptin despite treatment with metformin or a sulfonylurea and where a combination of metformin and a sulfonylurea is contraindicated or not tolerated. Listing was recommended on a cost-minimisation basis against rosiglitazone with the equi-effective doses being sitagliptin 100 mg daily and rosiglitazone 8 mg daily. A streamlined authority listing was sought, but sitagliptin was considered as a new class of drug and therefore not eligible for listing as a streamlined authority item.

In the same consideration, the PBAC rejected a proposal to list sitagliptin for use in type 2 diabetes in combination with metformin where metformin treatment alone provides inadequate control, and in the absence of a sulfonylurea contraindication or intolerance. Rejection was on the basis of uncertain evidence of a clinically relevant benefit over the comparator, sulfonylureas, and because of the resulting highly uncertain cost-effectiveness.

Listing of sitagliptin was effective from 1 August 2008.

Ezetimibe with simvastatin (Vytorin)

At the November 2008 meeting the PBAC considered a submission seeking recommendation under subsection 101(4AC) of the National Health Act 1953 that fixed dose combination (FDC) ezetimibe/simvastatin (Vytorin) provides significant improvement in patient compliance over its components. The PBAC advised that the submission provided a sufficient basis to conclude that FDC ezetimibe/simvastatin provides significant improvements in patient compliance

Compliance to Medicines Working Group (CMWG)

Subsequent to this decision, the PBAC requested that the Compliance to Medicines Working Group (CMWG) be established to gather information from experts and published literature on

methods for evaluating and interpreting evidence used to support claims that combination products improve consumer compliance and health outcomes. The CMWG reported to the April 2010 Special PBAC meeting, at which time the PBAC endorsed all the recommendations in the CMWG report.

Ezetimibe with atorvastatin

At the July 2012 meeting, the PBAC considered a submission requesting listing of ezetimibe with atorvastatin in FDC for and as a co-pack. The submission requested exemption under subsection 101(4AC) of section 84AH of the *National Health Act 1953.* The ratified short minutes for this consideration state:

> "The PBAC also noted that the approach for measuring compliance set out in the Compliance to Medicines Working Group Report to the PBAC had not been addressed, and considered that any future submission seeking PBAC advice to the Minister of a compliance benefit relating to the co-pack should address this approach."

3. Registration Status

The fixed dose combination (FDC) sitagliptin/simvastatin was TGA registered on 5 December 2012 for adult patients with type 2 diabetes mellitus in whom treatment with both sitagliptin and simvastatin is indicated according to the separate indications of these drugs.

4. Listing Requested and PBAC's View

Authority required (STREAMLINED)

For use in patients with type 2 diabetes who are currently receiving treatment with simvastatin; and who satisfy the criteria for prescribing DPP-4 inhibitors.

For PBAC's view, see Recommendations and Reasons.

5. Clinical Place for the Proposed Therapy

The submission stated that fixed dose combination (FDC) sitagliptin/simvastatin will provide a clinical alternative for patients who are currently treated with simvastatin and (i) a single anti-glycaemic treatment and would have otherwise been prescribed sitagliptin as add on dual antiglycaemic therapy or (ii) are controlled on dual oral anti-glycaemic therapy containing sitagliptin and would benefit from a FDC tablet.

6. Comparator

The submission nominated the corresponding doses of the individual components (sitagliptin and simvastatin) given concomitantly as the main comparator. The PBAC considered this to be appropriate.

7. Clinical Trials

To support the claim of equivalent efficacy and safety the submission presented two bioequivalence trials (P255 and P153) comparing FDC sitagliptin/simvastatin with its individual components in 224 healthy patients aged 18 to 55 years. The submission did not include any clinical trials of sitagliptin/simvastatin FDC in patients with type 2 diabetes.

The submission also presented data to support a claim of improved compliance of the FDC compared to its components.

8. Results of Trials

The results of the bioequivalence trials are summarised in the table below. Based on these data, the submission stated that all strengths of the sitagliptin/simvastatin FDC demonstrated bioequivalence when compared to the individual components.

Geometric Mean Ratio (GMR) of the pharmacokinetic properties of the FDC sitagliptin/simvastatin relative to the individual components

Trial P255 (100 sita + 10 simva/ 100/10 fixed dose sita/ simva)	**N**	**Estimated GMR (FDC/co-administration) (90% CI)**
Sitagliptin		
$AUC_{0-\infty}$	94	1.01 (0.99, 1.02)
AUC_{0-last}	94	1.01 (1.00,1.03)
C_{max}	95	1.03 (0.98,1.07)
Simvastatin		
AUC_{0-last}	95	1.07 (0.99,1.16)
C_{max}	95	1.13 (1.05, 1.21)
Simvastatin acid[a]		
AUC_{0-last}	95	1.03 (0.96, 1.11)
C_{max}	95	1.04 (0.97, 1.12)
Trial P153 (100 sita + 10 simva/ 100/10 fixed dose sita/ simva)	**N**	**Estimated GMR (FDC/co-administration) (95% CI)**
Sitagliptin		
$AUC_{0-\infty}$	94	0.99 (0.98, 1.00)
AUC_{0-last}	94	0.99 (0.98, 1.00)
C_{max}	95	0.98 (0.94,1.02)
Simvastatin		
AUC_{0-last}	95	0.99 (0.93,1.05)
C_{max}	95	0.98 (0.92, 1.06)
Simvastatin acid		
AUC_{0-last}	95	0.93 (0.87, 0.98)
C_{max}	95	0.95 (0.88, 1.02)

Abbreviations: sita = sitagliptin; simva = simvastatin.

[a]After oral ingestion, simvastatin, which is an inactive lactone, is hydrolysed to the corresponding active metabolite form beta-hydroxyacid (simvastatin acid).

In both trials (P255 and P153), no serious clinical or laboratory adverse event (AE) were reported and no subject discontinued or died due to an AE. AEs were evenly distributed across the treatment periods in both trials.

The submission stated that a search of the literature failed to identify any studies of the long term safety of FDC sitagliptin/simvastatin. The submission did not declare whether any studies on long term safety of concomitant use of sitagliptin and simvastatin were investigated.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

Based on bioequivalence trials P255 and P153, the submission claimed that sitagliptin/simvastatin FDC is equivalent in terms of comparative effectiveness and safety compared to its individual components (sitagliptin and simvastatin).

The PBAC considered the data presented in the submission adequately supported the claim of equivalence of sitagliptin plus simvastatin FDC in terms of comparative effectiveness and safety compared to the corresponding individual components taken concomitantly.

10. Economic Analysis

Based on the claim of non-inferiority, the submission presented a cost-minimisation analysis.

Based on the bioequivalence studies, the submission assumed that FDC sitagliptin/simvastatin 100 mg/40 mg, 20 mg or 10 mg taken once daily is equi-effective with the corresponding strengths of the components taken concomitantly once daily.

For PBAC's view, see Recommendations and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of packs dispensed of the sitagliptin/simvastatin FDC products to be in the range of 10,000-50,000 in year 5.

The accuracy of the submission's estimates of number of prescriptions per year, was dependent on the acceptance of the submission's assumptions regarding market growth of simvastatin and oral antihyperglycaemic therapies (given the ageing population and increased prevalence of type 2 diabetes) and whether the proportion of patients who would substitute from the various sources are reasonable.

The PBAC noted the concerns of the Economics Sub-Committee (ESC) and the Drug Utilisation Sub-Committee (DUSC) regarding the submission's likely underestimate of usage of sitagliptin with simvastatin FDC. The PBAC considered that the addition of a fixed dose combination of sitagliptin with simvastatin may potentially change the current growth in utilisation of gliptins. The PBAC considered that sitagliptin with simvastatin FDC is likely to replace some use of both products in the current gliptin and statin market and provide an alternative to the individual components and other drugs with both classes. The PBAC therefore requested DUSC to review this FDC in conjunction with other FDCs.

The estimated total net cost to the PBS is less than $10 million per year.

Although the FDC appears to be cheaper than the therapies administered concomitantly when the DPMQ is considered, there is a net overall cost to Government as the removal of the average patient co-payment when going from two to one medications exceeds any savings from the removal of a dispensing fee.

The submission claimed that the cost to Government was an overestimate because the price of FDC sitagliptin/simvastatin and sitagliptin only have been adjusted to reflect the change to the DPP4 inhibitor prices that will occur effective 1 August 2012, while the prices for vildagliptin and saxagliptin have not been adjusted. Recalculation of these during evaluation showed that using the 1 August 2012 prices of vildagliptin ($96.71) and saxagliptin ($90.70) increased the net cost to the PBS compared to the submission's estimates.

12. Recommendation and Reasons

The PBAC recommended listing sitagliptin with simvastatin 100 mg sitagliptin with 10 mg or 20 mg or 40 mg simvastatin fixed dose combination (FDC) tablet on the PBS as an Authority

Required (Streamlined) listing for diabetes and hypercholesterolaemia on a cost-minimisation basis with sitagliptin and simvastatin taken concomitantly.

The PBAC agreed that the corresponding doses of sitagliptin and simvastatin taken concomitantly, chosen as the comparator in the submission is appropriate.

The submission proposed a restriction requiring patients to be currently receiving treatment with simvastatin and who satisfy the criteria for prescribing DPP-4 inhibitors. The PBAC considered that the proposed restriction should be replaced by a restriction which requires patients to meet the prescribing criteria of drugs in the same class as sitagliptin and simvastatin (i.e. DPP-4 inhibitors and statins respectively).

The PBAC considered that the data from the bioequivalence trials (P255 and P153) presented in the submission adequately supported the claim of equivalence of sitagliptin plus simvastatin FDC in terms of comparative effectiveness and safety compared to the corresponding individual components taken concomitantly.

The submission presented a claim of non-inferiority based on the cost-minimisation analysis. This was considered appropriate by the PBAC.

The PBAC noted the following concerns with respect to the guidelines for FDCs:

- Criterion (d) requires that the doses of the listed component products and the proposed combination should be consistent. The PBAC noted that the sitagliptin and simvastatin FDC is not being produced in combination with sitagliptin 50 mg or 25 mg, being therefore unsuitable for patients with moderate to severe renal insufficiency. Additionally, the FDC will not be produced in combination with the lowest (5 mg) and highest (80 mg) strengths of simvastatin. The PBAC considered that excluding the highest dose of simvastatin was appropriate, given the safety issues in relation to the use of this strength noted by the TGA.
- Criterion (e) requires that there be additive (not necessarily synergistic) beneficial effectiveness of the components. The PBAC considered that the submission did not demonstrate additive benefits of FDC sitagliptin/simvastatin.
- Criterion (f) requires that the combination not encourage or result in an inappropriate increase in overall utilisation of the components, nor inappropriate use of one or both components in specific patient groups. The PBAC considered that there is a risk that sitagliptin may be used earlier in the treatment algorithm than specified in the PBS restriction (see below).
- Criterion (g) requires that the combination product not result in inappropriate dosing of either component, nor contain components which require individual dose titration. The PBAC considered that on balance the risk of inappropriate dosing with a sitagliptin/simvastatin FDC was low.
- Criterion (h) requires that the combination product not result in unnecessary proliferation of product and/or dose forms. The PBAC was not convinced of a pressing clinical need for a sitagliptin/simvastatin FDC but accepted that there may be a need to reduce pill burden in some patients with diabetes who require a statin.

The PBAC noted the concerns of the ESC and the DUSC regarding the submission's likely underestimate of usage of sitagliptin with simvastatin FDC. The PBAC considered that the addition of a fixed dose combination of sitagliptin with simvastatin may potentially change

the current growth in utilisation of gliptins. The PBAC considered that sitagliptin with simvastatin FDC is likely to replace some use of both products in the current gliptin and statin market and provide an alternative to the individual components and other drugs with both classes. The PBAC therefore requested DUSC to review this FDC in conjunction with other FDCs.

The PBAC noted the sponsor's withdrawal of a compliance claim under Subsection 101(4AC). The PBAC noted and concurred with the DUSC advice that the claim of improved compliance was based on poor quality evidence that does not meet the standards of the PBAC Compliance to Medicines Working Group Report and was not specifically related to for sitagliptin/simvastatin. Additionally the PBAC noted that the two meta-analyses presented provided insufficient detail to assess applicability to the PBS population, the vast majority of the trials having been conducted in countries with health care systems that differ significantly from Australia. Overall, the PBAC considered that the Vytorin III study, which was part of the submission to the July 2012 PBAC for ezetimibe with atorvastatin, was insufficient to support a claim of improved compliance.

Overall, notwithstanding these concerns about the submission in relation to the FDC guidelines, the PBAC considered that the requirements under the *National Health Act* for recommending listing of a product were met, provided that, as claimed in the submission the listing is cost neutral to the PBS. The PBAC recommended, as noted above that if this is not the case a review of the listing may be appropriate following the DUSC review of utilisation.

The PBAC recommended the 20 day safety net rule should apply.

The PBAC recommended sitagliptin with simvastatin FDC is suitable for inclusion in the medicines for prescribing by nurse practitioners within collaborative arrangements.

Recommendation:
Sitagliptin with simvastatin, tablets, 100 mg–10 mg, 100 mg–20 mg and 100 mg–40 mg

Restriction:

Authority Required (STREAMLINED)
Diabetes mellitus type 2 and hypercholesterolaemia

- Patient must meet the criteria set out in the General Statement for Lipid-Lowering Drugs;
- The treatment must be in combination with metformin; OR
- The treatment must be in combination with a sulfonylurea;
- Patient must have a contraindication to a combination of metformin and a sulfonylurea; OR
- Patient must not have tolerated a combination of metformin and a sulfonylurea; and
- Patient must have, or have had, a HbA1c measurement greater than 7% prior to the initiation of a dipeptidy peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like-peptide-1 despite treatment with either metformin or a sulfonylurea; OR
- Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period prior to initiation with a gliptin, a glitazone or a glucagon-like peptide-1 despite treatment with either metformin or a sulfonylurea.

Prescriber Instructions:

- The date and level of the qualifying HbA1c measurement must be or must have been documented in the patient's records at the time treatment with a gliptin, glitazone or a glucagon-like peptide-1 is initiated.
- The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone or a glucagon-like peptide-1 is or was initiated.
- 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
- 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 or a glucagon-like peptide-1, must be documented in the patient's medical records.

Note

- The treatment must not be in combination with a thiazolidinedione (glitazone) or glucagon-like peptide-1.

Max Qty:	28
Rpts:	5

13. 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.

14. Sponsor's Comment

The sponsor did not provide further comment.