The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**alogliptin (Vipidia®)** is not recommended for use within NHS Scotland.

**Indication under review:** For adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control in combination with other glucose lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Treatment with alogliptin reduces glycosylated haemoglobin, HbA1c, significantly more than placebo when used in combination with metformin or sulfonylurea. There are no clinical studies of alogliptin, as triple therapy, in combination with metformin and sulfonylurea.

The submitting company did not present sufficiently robust clinical and economic analysis to gain acceptance by SMC.

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

**Chairman,**
Scottish Medicines Consortium
**Indication**
In adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control in combination with other glucose lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

**Dosing Information**
The recommended dose is 25mg once daily, with or without food. Patients with moderate renal impairment (creatinine clearance between 30 and 50mL/min) should take 12.5mg daily, and those with severe, or end-stage renal disease are recommended to take 6.25mg daily.

When alogliptin is used in combination with metformin and/or a thiazolidinedione, the dose of metformin and/or the thiazolidinedione should be maintained, and alogliptin administered concomitantly.

When alogliptin is used in combination with a sulphonylurea or insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia.

**Product availability date**
27 January 2014

**Summary of evidence on comparative efficacy**

Type 2 diabetes mellitus is a chronic, progressive disease involving insulin resistance, impaired insulin secretion, and increased glucose production. Alogliptin inhibits the enzyme dipeptidyl peptidase-4 (DPP-4), preventing the degradation of incretin hormones, which are released from gut cells in response to a meal. These hormones stimulate insulin release and attenuate glucagon secretion in response to raised blood glucose levels.

The company has requested that SMC considers alogliptin when positioned for use where a DPP-4 inhibitor is considered appropriate in type 2 diabetes mellitus, in the following settings:
- Dual therapy in combination with metformin;
- Dual therapy in combination with a sulfonylurea;
- Triple therapy in combination with metformin and a sulfonylurea.

Evidence for alogliptin as dual therapy in combination with metformin or sulfonylurea includes three randomised, double-blinded, phase III studies.1,2,3,4

Two placebo-controlled studies provided evidence of alogliptin use over 26 weeks.3,4 They recruited adults with type 2 diabetes mellitus with inadequate glycaemic control (HbA1c 7.0% to 10.0%) despite treatment with a stable dose of metformin (≥1,500mg per day),3 or sulfonylurea.4 Patients had body mass index between 23 and 45kg/m².

In the metformin study, after a placebo run-in, patients continued open-label metformin and were randomised (stratified by country and baseline HbA1c) in a 2:2:1 ratio to alogliptin 25mg daily (n=210), alogliptin 12.5mg daily (n=213), or placebo (n=104). No dose adjustment of metformin was permitted and rescue treatment for hyperglycaemia was indicated according to
In the sulfonylurea study, a run-in/stabilisation phase involved a switch to open-label glibenclamide at a dose equivalent to the patient’s pre-study sulfonylurea, ≥10mg daily (≥5mg daily if tolerability issues) and commencement of placebo run-in (4 weeks). Eligible patients continued open-label glibenclamide and were randomly allocated (stratified by geographical region and baseline HbA1c) in a 2:2:1 ratio to alogliptin 25mg daily (n=198), alogliptin 12.5mg daily (n=203), or placebo (n=99) for 26 weeks. The glibenclamide dose could be reduced once weekly in 2.5mg increments to resolve hypoglycaemia. Rescue treatment (for hyperglycaemia) was indicated according to pre-specified rules. Results for the two studies’ primary outcomes and selected secondary endpoints are presented in the table below.

Table 1: Efficacy outcome results of placebo-controlled studies analysed in the FAS using LOCF

<table>
<thead>
<tr>
<th></th>
<th>Dual therapy with metformin</th>
<th>Dual therapy with sulfonylurea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alogliptin 25mg</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>Alogliptin 25mg</td>
<td>Placebo</td>
</tr>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS mean change in HbA1c from baseline to week 26</td>
<td>-0.6% p&lt;0.001</td>
<td>-0.1% p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>-0.53% p&lt;0.001</td>
<td>0.01%</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of patients achieving HbA1c ≤7.0%</td>
<td>44% p&lt;0.001</td>
<td>18% p&lt;0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35%</td>
</tr>
<tr>
<td>Change in body weight from baseline to week 26</td>
<td>placebo-adjusted LS mean = -0.3kg (95% CI: -0.9 to 0.4)</td>
<td>0.68kg p=0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.20kg</td>
</tr>
</tbody>
</table>

CI=confidence interval, LS=least squares, FAS=full analysis set, LOCF=last observation carried forward

ENDURE was a multi-national, randomised, double-blind, controlled study which followed patients over 104 weeks of treatment with either alogliptin (25mg or 12.5mg daily) or glipizide, in combination with open-label metformin. It recruited adults (18 to 80 years of age); with body mass index between 23 and 45kg/m², or 20 and 35kg/m² if Asian; and type 2 diabetes mellitus with inadequate glycaemic control despite treatment with a stable dose of metformin. Prior to allocation to treatment group, patients not on documented maximum tolerated dose or at least 1,500mg/day of metformin underwent a titration phase over eight weeks, after which HbA1c was required to be between 7.0 and 9.0%. Patients were randomised (stratified by country, baseline HbA1c and need for metformin titration) in a 1:1:1 ratio to alogliptin 25mg daily (n=885), alogliptin 12.5mg daily (n=880) or glipizide 5mg daily titrated at 4-weekly intervals to 20mg (n=874). Glipizide could be down-titrated for hypoglycaemia. After week 20, hyperglycaemic rescue was determined by HbA1c results.

The primary outcome measure was change from baseline to week 104 in HbA1c. The study was designed to test in a fixed sequence for non-inferiority (pre-specified margin of 0.3%) of alogliptin 25mg then 12.5mg with glipizide, followed by test for superiority of alogliptin (25mg then 12.5mg) with glipizide. The primary analyses were conducted in the per protocol population (approximately 40% of the randomised population) using LOCF. At week 104, the change from baseline in HbA1c was -0.72% in the alogliptin 25mg group (n=382), -0.68% in the alogliptin 12.5mg group (n=371) and -0.59% in the glipizide group, mean daily dose 5.2mg (n=336). The least squares mean difference between alogliptin 25mg and glipizide was -0.13% (1-sided 98.75% CI: infinity to -0.006). For the comparison between alogliptin 12.5mg and glipizide, the least squares mean difference was -0.09 (1-sided 98.75% CI: infinity to 0.035).

Secondary endpoints were analysed in the FAS, defined as all randomised patients who took at least one dose and who had baseline and at least one post-baseline efficacy measurement. For
the recommended dose of 25mg daily, the proportion of patients achieving an HbA1c ≤7.0% was 48% (420/878) compared with glipizide 43% (366/870), p=0.004.

There are no clinical studies for alogliptin as triple therapy, in combination with metformin and sulfonylurea.

**Summary of evidence on comparative safety**

In the ENDURE study treatment emergent adverse events were reported in similar proportions of patients in each treatment group (78 to 80%), leading to discontinuation in 8.4% (74/878) of patients in the alogliptin 25mg group and 9.4% (82/870) in the glipizide group. The adverse event profile was similar between the groups, with the notable exception of hypoglycaemia: 1.4% (12/878) in the alogliptin 25mg group compared with 23% (202/870) in the glipizide group. Severe episodes (in which external assistance was required and blood glucose was <60mg/dL) occurred in no patients in the alogliptin 25mg group and five (0.6%) in the glipizide group.1,2

In general, the safety profile of alogliptin 25mg plus metformin was similar to that of placebo plus metformin. There was a low incidence of hypoglycaemic events, reported in five patients in total (3 in the placebo group, and 2 in the alogliptin 12.5mg group). There were no instances of severe hypoglycaemia.3

In the sulfonylurea combination, a placebo-controlled study, a slightly higher proportion of patients in the alogliptin groups reported at least one adverse event during the study (approximately 63%) compared with placebo (54%). Treatment-related adverse events were experienced by 18% of alogliptin 25mg patients, 15% of alogliptin 12.5mg patients, and 10% of placebo patients. Adverse events lead to study discontinuation in 2.0 to 2.5% of patients. Hypoglycaemic events occurred in a small proportion of patients: 9.6% (19/198) alogliptin 25mg patients, 16% (32/203) alogliptin 12.5mg patients and in 11% (11/99) placebo patients. There were only three episodes of hypoglycaemia severe enough to require assistance: one in the placebo group and two in the alogliptin 12.5mg group.4

The EXAMINE study was a multicentre, randomised, double-blind, placebo-controlled study which recruited patients treated with anti-diabetic medicines for type 2 diabetes, who were at high risk of cardiovascular disease and inadequate glycaemic control.5 Patients were randomised to either alogliptin, dose dependent upon baseline renal function (n=2,701) or placebo (n=2,679). After a median duration of exposure of approximately 18 months (533 days), the proportion of patients in each group meeting the primary endpoint (a composite of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke) was 11.3% in the alogliptin group and 11.8% in the placebo group. The associated hazard ratio was 0.96 (1-sided 95% CI: 1.16). Non-inferiority of alogliptin was declared since the upper limit of the 1-sided CI was less than the pre-specified margin of 1.3.
Summary of clinical effectiveness issues

Alogliptin is the fifth DPP-4 inhibitor to come to market. The company has requested that SMC considers alogliptin only where a DPP-4 inhibitor is considered appropriate, in the following settings:

- Dual therapy in combination with metformin, when metformin alone, together with diet and exercise does not provide adequate glycaemic control in patients for whom the addition of a sulfonylurea is inappropriate
- Dual therapy in combination with a sulfonylurea when sulfonylurea alone, together with diet and exercise does not provide adequate glycaemic control in patients for whom the addition of metformin is inappropriate.
- Triple therapy in combination with metformin and a sulfonylurea when dual therapy with these medicinal products, together with diet and exercise does not provide adequate glycaemic control.

Saxagliptin, sitagliptin and vildagliptin have marketing authorisations in the above settings, whereas linagliptin is not licensed for use as dual therapy in combination with sulfonylurea.

Clinical experts consulted by SMC have advised that sitagliptin is the predominant DPP-4 inhibitor prescribed in Scotland and this is supported by Scottish Prescribing data.

The primary outcome in all three efficacy studies was the change in HbA1c from baseline to study endpoint. HbA1c is a measure of glycaemic control. In patients with type 2 diabetes, reduction in HbA1c is associated with a reduction in microvascular and macrovascular complications. Treatment guidelines recommend HbA1c targets in the treatment of diabetes. The way in which HbA1c results are expressed in the UK has changed recently; results are now reported as mmol/mol rather than as a percentage. The equivalent of the HbA1c targets of 6.5% and 7.0% are 48mmol/mol and 53mmol/mol in the new units.

Alogliptin in combination with metformin or sulfonylurea was associated with a modest but clinically significant improvement in glycaemic control (a placebo-adjusted reduction in HbA1c of approximately 0.5%). In the ENDURE study, the mean dosage of the comparator glipizide during the double-blind period was low (5.2mg daily). For this reason, and due to low baseline HbA1c, the European Medicines Agency did not consider the non-inferiority (as add-on therapy to metformin) of alogliptin to glipizide to be demonstrated.

The ENDURE study had a high proportion of patient drop-out (45 to 51% of patients per group), and there was significant drop-out in the placebo controlled studies. The main reason for drop-out in all three studies was lack of efficacy and the requirement for hyperglycaemic rescue.

The three pivotal studies provide evidence for the use of alogliptin in the dual therapy setting: combination with metformin when metformin with diet and exercise is insufficient, and when sulfonylurea is inappropriate; and in combination with sulfonylurea when sulfonylurea with diet and exercise is insufficient and when metformin is inappropriate. The two studies in combination with metformin did not recruit patients who specifically could not take sulfonylurea, and the sulfonylurea combination study did not specify that metformin was inappropriate for its recruited patients.
A further limitation to the evidence base is the absence of any studies of alogliptin in combination with metformin and sulfonylurea. The SPC states “the safety and efficacy of alogliptin when used as triple therapy with metformin and a sulphonylurea have not been established”. Late in the submission assessment process, the company presented a post-hoc sub-group analysis of the EXAMINE study of patients who were taking metformin and sulfonylurea at baseline. The validity of these additional data was limited by several factors such as; no baseline characteristics or disposition data were presented; and the study allowed adjustment of background treatment.

There are no direct comparative data versus other DPP-4 inhibitors, so to support the economic case, the company presented several analyses for the proposed positioning; a Bayesian mixed-treatment comparison (MTC) of DPP-4 inhibitors when used in combination with metformin (38 studies); a MTC of DPP-4 inhibitors in combination with sulfonylurea (8 studies); and an Additive Effects Model used to estimate the efficacy of alogliptin in combination with metformin and sulfonylurea. The MTCs compared several outcomes; the change from baseline in HbA1c; the proportion of patients achieving HbA1c <7.0%; the change from baseline in body weight; and the incidence of hypoglycaemic events.

The results of the MTCs for dual therapy suggested alogliptin had similar efficacy and safety to the other DPP-4 inhibitors for the outcomes compared. However there are weaknesses associated with the relevance and credibility of the analyses that limit the validity of the company’s conclusion. The relevance is reduced by the inclusion of several studies in which patients were treatment naïve (i.e. not inadequately controlled on metformin or sulfonylurea monotherapy). Internal validity has been questioned with limitations in: the search strategy used to identify studies which failed to include one of the company’s pivotal studies in the metformin MTC; inclusion and exclusion criteria too broad for the indication under review such as previous anti-diabetic treatment history which lead to heterogeneity between the studies; notable variability in baseline HbA1c; combination of different doses of DPP-4 inhibitors used in the studies; inadequate reporting of checks for evidence consistency; and comparison of outcomes at different timepoints.

The efficacy of alogliptin in combination with metformin and sulfonylurea was estimated using an Additive Effects Model. The model made two assumptions:

- The efficacy of a DPP-4 inhibitor in combination with metformin and sulfonylurea can be estimated by a function of the constituent parts of the triple therapy
- Efficacy of the constituent parts of alogliptin triple therapy is equivalent to those of the constituent parts of the other DPP-4 inhibitor triple therapy combinations.

The model used the results of several MTCs of DPP-4 inhibitors (monotherapy, dual therapy with metformin, dual therapy with sulfonylurea, and triple therapy with metformin and sulfonylurea) to derive a weighting factor (β coefficient) that could be applied to the available data for alogliptin. The efficacy outcome estimated was change from baseline in HbA1c. The company concluded that the results of the model indicated that the addition of alogliptin to metformin and sulfonylurea as triple therapy would likely provide similar benefits to those of linagliptin, sitagliptin and vildagliptin. A statistical expert consulted by SMC questioned the validity of this novel approach, and its suitability to provide evidence for alogliptin as part of a triple therapy regimen. Furthermore, there are issues with the MTCs used to inform the model; the results of the monotherapy and dual therapy MTCs are considered to have low credibility (as described above for the dual therapy MTCs).
While additional analysis was submitted by the company after the New Drugs Committee to address some of these concerns, the committee concluded that this data required more assessment than could be undertaken at this stage in the process.

*Other data were also assessed but remain commercially confident*

### Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis of alogliptin as an alternative DPP-4 inhibitor for adult patients with type 2 diabetes mellitus when metformin or sulfonylurea alone, or dual therapy with metformin and sulfonylurea, together with diet and exercise, does not provide adequate glycaemic control. The analysis focused on the use of alogliptin in the following settings:

1) in combination with metformin (dual therapy) versus sitagliptin, saxagliptin and linagliptin in combination with metformin,
2) in combination with sulfonylurea (dual therapy) versus sitagliptin in combination with sulfonylurea,
3) in combination with metformin and sulfonylurea (triple therapy) versus sitagliptin and linagliptin in combination with metformin and sulfonylurea

The submitting company justified the comparators on the basis that they are the most commonly prescribed DPP-4 inhibitors. The analysis was based on a one year time horizon and was from an NHS perspective.

The data to support comparable efficacy were based on indirect comparisons between alogliptin and each of the other DPP-4 inhibitors in combination with metformin, sulfonylurea or metformin plus sulfonylurea. The company stated that the indirect comparisons suggested non-inferiority between alogliptin and the other DPP-4 inhibitors.

There were however no clinical studies that demonstrated the effectiveness of alogliptin as a triple therapy in combination with metformin and sulfonylurea, therefore an additive effects model was developed to estimate the likely treatment effect. The submitting company stated that the results of the additive effects model demonstrate that adding alogliptin to metformin and sulfonylurea as triple therapy would be likely to provide similar benefits to those of linagliptin, sitagliptin or vildagliptin when used as triple therapy in combination with metformin and sulfonylurea.

Only the drug costs of alogliptin, sitagliptin, saxagliptin and linagliptin were included in the analysis. The costs of metformin and sulfonylurea were assumed to be the same for each DPP-4 inhibitor and therefore not included.

The results showed the annual alogliptin cost per patient was estimated to be £346.75 compared with £433.57 for both sitagliptin and linagliptin and £411.93 compared with saxagliptin. The cost-minimisation analysis therefore showed that alogliptin would be cost-saving compared with sitagliptin, saxagliptin, or linagliptin, with annual savings per patient of £86.82 compared with both sitagliptin and linagliptin and savings of £65.18 compared with saxagliptin.

The key weakness associated with the analysis is the concern that comparable efficacy between alogliptin and the other DPP-4 inhibitors has not been demonstrated and this
undermines the results of the cost-minimisation analysis. Therefore, the economic case has not been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guideline Network (SIGN) published guideline 116 Management of diabetes A National Clinical Guideline in March 2010. It states that DPP-4 inhibitors may be used to improve blood glucose control in people with type 2 diabetes but notes that published studies for sitagliptin and vildagliptin have medium term follow up (maximum of two years) therefore the long term effects of these drugs on microvascular complications, cardiovascular disease and mortality are unknown. The treatment algorithm notes several options for second and third-line treatment of type 2 diabetes mellitus to be added in combination with metformin and/or sulfonylurea; additional oral anti-diabetic drugs, pioglitazone or DPP-4 inhibitors; or injections of GLP-1 analogues or commencement of insulin. Treatment should be continued if an individualised target is reached or the HbA1c falls at least 0.5% in 3 to 6 months.

The National Institute for Health and Care Excellence (NICE) published clinical guideline 87: Type 2 diabetes: the management of type 2 diabetes in May 2009. It recommends considering the addition of a DPP-4 inhibitor as second- or third-line therapy in specific circumstances.

The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) published a position statement “Management of Hyperglycaemia in type 2 diabetes: a patient-centred approach” in June 2012. This suggests a number of treatment options for triple therapy with no specific preference: choice is based on patient and drug characteristics.

Additional information: comparators

The DPP-4 inhibitors (linagliptin, saxagliptin, sitagliptin, and vildagliptin) have marketing authorisations for all three indications under review, with the exception of linagliptin which is not licensed for use as dual therapy in combination with a sulfonylurea.
### Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per year (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alogliptin</td>
<td>25mg orally once daily</td>
<td>346</td>
</tr>
<tr>
<td>Linagliptin*</td>
<td>5mg orally once daily</td>
<td>432</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>100mg orally once daily</td>
<td>432</td>
</tr>
<tr>
<td>Saxagliptin#</td>
<td>5mg orally once daily</td>
<td>411</td>
</tr>
<tr>
<td>Vildagliptin^</td>
<td>50mg orally twice daily (once daily when in dual therapy in combination with sulfonylurea) (206 if once daily)</td>
<td>413</td>
</tr>
</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 28 October 2013 except alogliptin (from company’s submission).

* Linagliptin does not have a marketing authorisation for use as dual therapy in combination with sulfonylurea.

# Saxagliptin is not recommended for use in NHS Scotland when used as dual therapy in combination with sulfonylurea. Triple therapy advice expected Dec 2013

^ Not recommended for use in triple therapy due to non-submission.

### Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 959 in year 1 rising to 7,416 in year 5 based on an assumed market share of 5% in year 1 and 30% in year 5.

The gross impact on the medicines budget was estimated to be £333k in year 1 and £2.57m in year 5. As other drugs were assumed to be displaced the net impact on the medicines budget is expected to be savings of £82k in year 1 and £634k in year 5.

Based on alogliptin use in dual therapy only, the submitting company estimated the population eligible for treatment to be 469 in year 1 rising to 3,625 in year 5 based on an assumed market share of 5% in year 1 rising to 30% in year 5.

The gross impact on the medicines budget was estimated to be £163k in year 1 and £1.26m in year 5. As other drugs were assumed to be displaced the net impact on the medicines budget impact is expected to be savings of £40k in year 1 and £310k in year 5.
The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.


2) Takeda Global Research & Development Center, Inc. Final Clinical Study Report. SYR-322_305. A multicenter, randomized, double-blind, active-controlled study to evaluate the durability of the efficacy and safety of alogliptin compared to glipizide when used in combination with metformin in subjects with type 2 diabetes. 22 March 2013.


This assessment is based on data submitted by the applicant company up to and including 15 January 2014.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*

http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.
Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.