# Scottish Medicines Consortium

## vildagliptin 50mg tablets (Galvus®) No. (571/09)
## Novartis Pharmaceuticals UK Ltd

04 September 2009

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 NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**vildagliptin (Galvus®)** is accepted for use within NHS Scotland for the treatment of type 2 diabetes mellitus as dual oral therapy in combination with a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea or for whom metformin is inappropriate due to contraindications or intolerance.

When added to a sulphonylurea, vildagliptin had a modest beneficial effect on glycated haemoglobin ($HbA_{1C}$).

Vildagliptin is also licensed for use in combination with metformin or thiazolidinedione drugs for the treatment of type 2 diabetes. SMC has already issued advice on use in combination with metformin. As this submission from the manufacturer related only to the use of vildagliptin in combination with a sulphonylurea, SMC cannot recommend the use of vildagliptin in combination with thiazolidinedione drugs.

Overleaf is the detailed advice on this product.

**Chairman,**
**Scottish Medicines Consortium**

## Indication

For the treatment of type 2 diabetes mellitus as dual oral therapy in combination with a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea or for whom metformin is inappropriate due to contraindications or intolerance.

## Dosing information

When used in dual combination with a sulphonylurea, the recommended dose of vildagliptin is 50mg once daily administered in the morning.

## Product availability date

March 2008

## Summary of evidence on comparative efficacy

Vildagliptin is a dipeptidyl peptidase type 4 (DPP-4) inhibitor that enhances the level of active incretin hormones (including glucagon-like peptide-1 (GLP-1)) thereby reducing blood glucose levels by increasing insulin secretion and reducing glucagon secretion.

One 24-week, multi-centre, randomised, double-blind, phase III, placebo-controlled study enrolled patients aged 18 to 80 years with inadequately controlled type 2 diabetes mellitus (glycated haemoglobin $HbA_{1C}$ 7.5 to 11%) despite at least three months of sulphonylurea monotherapy. At screening, patients not receiving glimepiride 4mg daily were switched to this sulphonylurea regimen for a 4-week run-in period, after which eligible patients (those with $HbA_{1C}$ 7.5 to 11%) were randomised to receive vildagliptin (50mg once daily), vildagliptin (50mg twice daily) or placebo as add-on therapy to glimepiride. Although the study included a vildagliptin 50mg twice daily group, results will not be presented for this group since it is higher than the recommended dose for combination therapy with a sulphonylurea. Patients were not permitted to receive antidiabetic rescue medication and if there was unsatisfactory therapeutic effect the patient discontinued the study. The glimepiride dose could be reduced to 2mg daily if hypoglycaemia occurred.

The primary efficacy endpoint was the mean change from baseline $HbA_{1C}$ at week 24 compared to placebo in the primary intention to treat (ITT) population and using last observation carried forward (LOCF) for patients who discontinued early. Secondary endpoints of note included the change from baseline in fasting plasma glucose (FPG) and the proportions of patients achieving pre-defined levels of $HbA_{1C}$ reduction.

A total of 515 patients were randomised and 408 comprised the primary ITT population. $HbA_{1C}$ levels decreased from a mean (±standard deviation [SD]) baseline of 8.5±0.9% by 0.58±0.10% in the vildagliptin group (n=132) compared with an increase of 0.07±0.09% from a mean baseline of 8.5±1.0 in the placebo group (n=144), resulting in a significant between group difference of 0.64±0.13%. Significantly more vildagliptin than placebo treated patients achieved a reduction in $HbA_{1C}$ to <7% (21% versus 12% respectively) and a reduction in $HbA_{1C}$ of ≥0.7% (47% versus 19% respectively).

At week 24, the mean (±SD) FPG had decreased by 0.3±0.2mmol/L from a mean baseline of 10.5±3.0mmol/L in the vildagliptin group and had increased by 0.2±0.2mmol/L from a mean baseline of 10.3±2.9mmol/L in the placebo group. The between group difference in mean change in FPG did not reach statistical significance.

## Summary of evidence on comparative safety

Adverse events were reported by 67% of vildagliptin and 64% of placebo-treated patients. The majority were of mild to moderate severity and were not suspected to be related to study drug. Hypoglycaemia was reported in 1.2% (2/170) vildagliptin and 0.6% (1/176) placebo patients. Body weight decreased slightly in both the vildagliptin (0.1kg) and placebo groups (0.4kg) with no significant difference between the groups.

## Summary of clinical effectiveness issues

The size of the additional effect on $HbA_{1C}$ when vildagliptin was added to glimepiride was relatively modest but was significantly larger than in the placebo group and was considered clinically relevant.

The study only assessed efficacy and tolerability to week 24. As discussed in a Cochrane review of this drug class, inhibition of the DPP-4 enzyme may influence immune function, so additional long-term safety data are required. Long-term studies are also needed to determine the effect of vildagliptin on morbidity and mortality.

There are currently no data comparing vildagliptin to other DPP-4 inhibitors as add-on therapy to a sulphonylurea. The company have performed an indirect comparison with sitagliptin suggesting similar efficacy and tolerability when added to glimepiride but head-to-head clinical data are needed. Available data assess vildagliptin as add-on therapy to glimepiride and there are no data in combination with other more commonly used sulphonylureas.

The recommended dose for vildagliptin when used in combination with a sulphonylurea (50mg daily) is lower than the dose recommended for use in combination with metformin or a thiazolidinedione (50mg twice daily) which could introduce the potential for confusion.

Unlike vildagliptin, the other DPP-4 inhibitor, sitagliptin, is also licensed to improve glycaemic control in combination with a sulphonylurea and metformin (triple therapy) when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.

Vildagliptin, unlike sitagliptin, requires hepatic monitoring. The sulphonylurea glimepiride also requires hepatic monitoring so when used in this combination, it will not result in additional monitoring. However when used in combination with other more commonly used sulphonylureas, vildagliptin will result in extra monitoring.

## Summary of comparative health economic evidence

The manufacturer presented a cost-minimisation analysis comparing vildagliptin 50mg once daily with sitagliptin 100mg once daily, both used in combination with sulphonylurea in patients who are uncontrolled on sulphonylurea alone. The comparator was appropriate but it should be noted that no comparison with thiazolidinediones was presented. The analysis was conducted for a one year time horizon only.

The evidence of comparable efficacy, as required for a cost-minimisation analysis, was derived from a simple indirect comparison of the two treatments. This was based on the results of the pivotal trial for vildagliptin and a published study for sitagliptin.

While there were some differences between the studies used, the analysis did suggest that the treatments resulted in similar falls in HbA1c. Only drug acquisition costs for vildagliptin and sitagliptin and the cost of liver function tests for patients prescribed vildagliptin were included in the analysis. The costs of sulphonylurea were not included on the implicit assumption that this cost would be the same between treatments.

The results of the analysis indicated that the annual cost of vildagliptin was £287.01 compared to £433.57 for sitagliptin, and therefore that vildagliptin would be preferred on cost-minimisation grounds.

Several limitations of the analysis should be noted:

- No sensitivity analysis was provided but it is clear that if vildagliptin were used at a dose of 100mg per day (as per one of the groups in the pivotal study) then vildagliptin would no longer be the more cost-effective treatment;
- The evidence base to support the equivalence of vildagliptin and sitagliptin was based on a simple indirect comparison rather than a head-to-head study; and
- Other comparator treatments could have been considered such as thiazolidinediones and therefore the cost-effectiveness of vildagliptin compared to these treatments is not known.

Despite these issues the economic case was demonstrated for patients in whom the addition of a DPP-4 inhibitor is appropriate.

## Summary of patient and public involvement

A Patient Interest Group Submission was not made.

## Additional information: guidelines and protocols

The National Institute for Health and Clinical Excellence (NICE) produced a clinical guideline (number 66) in May 2008 entitled “Type 2 diabetes: the management of type 2 diabetes”. NICE also produced a short clinical guideline (number 87) in May 2009 entitled “Type 2 diabetes: newer agents” which recommends that DPP-4 inhibitors should be considered as second-line therapy to first-line sulphonylurea monotherapy when control of blood glucose remains or becomes inadequate ($HbA_{1C} \geq 6.5\%$ or other higher level agreed with the individual) if the person does not tolerate metformin or metformin is contraindicated. DPP-4 inhibitors should only be continued if the person has had a beneficial metabolic response (a reduction of $\geq 0.5\%$ in $HbA_{1C}$ in six months).

## Additional information: comparators

The other DPP-4 inhibitor, sitagliptin, the thiazolidinediones (pioglitazone and rosiglitazone), acarbose and exenatide are all licensed for use in combination with a sulphonylurea in patients with type 2 diabetes mellitus.

## Cost of relevant comparators

| Drug | Dose regimen | Cost per year (£) |
|---|---|---|
| **vildagliptin** | **50mg daily orally** | **206** |
| exenatide | 5 to 10 micrograms twice daily subcutaneously | 828 |
| sitagliptin | 100mg daily orally | 432 |
| rosiglitazone | 4mg once or twice daily (or 8mg once daily) orally | 260 to 520 |
| pioglitazone | 15 to 45 mg once daily orally | 185 to 480 |
| acarbose | 50mg once daily to 200mg three times daily orally | 25 to 281 |

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 18 June 2009.

## Additional information: budget impact

The manufacturer estimated that the gross budget impact (including liver function tests) was £6k in year one rising to £23k in year five. The net budget impact, given displacement of some prescribing of sitagliptin was a saving of £3k in year one rising to a saving of £12k in year five. Two hundred and three patients in year one are assumed to be eligible for treatment with either vildagliptin or sitagliptin, rising to 263 patients by year five. Market share for vildagliptin was assumed to be 10% in year one rising to 30% by year five. The budget impact estimates did not assume any switch in prescribing from thiazolidinediones.

***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.*

*This assessment is based on data submitted by the applicant company up to and including 14 August 2009.*

*Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.*

*The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.*

Garber AJ, Foley JE, Banerji MA et al. Effects of vildagliptin on glucose control in patients with type 2 diabetes inadequately controlled with a sulphonylurea. Diabetes Obesity and Metabolism 2008;10:1047-56

European Medicines Agency (EMEA). European public assessment report (EPAR) for Drug vildagliptin. www.emea.europa.eu /humandocs/PDF/EPAR/galvus/H-771-en6.pdf

Ritcher B, Bandeira-Echtler E, Bergerhoff K et al. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2008; Issue 2 Article number CD006739