Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

vildagliptin 50mg tablets (Galvus®) SMC No. (826/12)

Novartis

07 December 2012

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 restricted use within NHS Scotland.

Indication under review: treatment of type 2 diabetes mellitus in adults as monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.

SMC restriction: for use in patients for whom both metformin and sulphonylureas are inappropriate due to contraindications or intolerance.

In two comparator controlled studies the non-inferiority of vildagliptin to first-line oral anti-diabetic agents was not shown. A network meta-analysis demonstrated similar reductions in HbA1c at 24 weeks for vildagliptin versus another dipeptidyl peptidase 4 (DPP-4) inhibitor.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

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Indication

The treatment of type 2 diabetes mellitus in adults as monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.

Dosing Information

Vildagliptin 50mg in the morning and in the evening.

Product availability date

30 January 2012

Summary of evidence on comparative efficacy

Vildagliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor. SMC has previously accepted vildagliptin for use in combination with metformin or a sulphonylurea. The submission under review relates to an extension to the marketing authorisation, to include vildagliptin use as monotherapy in patients for whom metformin is inappropriate. The submitting company has requested that SMC considers vildagliptin when positioned for use in patients for whom both metformin and sulphonylureas are inappropriate due to contraindications or intolerance and when a DPP-4 inhibitor is an appropriate treatment option. Monotherapy treatment options other than metformin and sulphonylureas include sitagliptin, pioglitazone and repaglinide.

Evidence to support the monotherapy indication comes from two, double-blind, randomised multi-centre, active controlled studies in drug-treatment-naïve patients with type 2 diabetes.[1,2] Enrolled patients had a glycosylated haemoglobin (HbA1c) of 7.5% to 11.0% at screening and a fasting plasma glucose (FPG) of <15mmol/L. Patients were considered drug-naive when they had received no oral anti-diabetic drugs for at least 12 weeks prior to screening and no oral anti-diabetic drugs for more than three consecutive months at any time in the past. The primary endpoint in both studies was the change in HbA1c from baseline to study endpoint.

In one study (2309), a total of 780 patients were randomised 2:1 to vildagliptin 50mg twice daily or metformin 1,000mg twice daily for 52 weeks.[1] Non-inferiority of vildagliptin relative to metformin was established if the upper limit of the 95% confidence interval (CI) for the between treatment difference in HbA1c did not exceed 0.4% and was analysed in the intent to treat population. In the other study (2310), 1092 patients were randomised equally to vildagliptin 50mg twice daily or gliclazide at a dose up to 320mg daily for 104 weeks.[2] A non-inferiority margin of 0.3% was pre-specified and the per protocol population was used.

In both studies, non-inferiority was not demonstrated for vildagliptin versus the comparator. Also, in study 2309 there was a significant difference in mean change in HBA1c for metformin versus vildagliptin. Results for the primary endpoint are displayed in the table below.

Table: mean change in HbA1c from baseline to study endpoint (primary endpoint) for studies 2309 and 2310

	Study 2309		**Study 2310**	
	vildagliptin	metformin	Vildagliptin	gliclazide
N	511 (ITT)	249 (ITT)	409 (PP)[3]	409 (PP)
Mean HbA1c at baseline	8.7%	8.7%	8.5%	8.7%
AMD (±standard deviation) from baseline to study endpoint*	-1.0 (±0.1%)	-1.4 (±0.1%)	-0.5% (NR)	-0.6% (NR)
Difference (95% CI), p value	NR (0.28% to 0.65%), p<0.001		0.13% (-0.06% to 0.33%), NR	

AMD; adjusted mean difference; * 52 weeks for study 2309 and 104 weeks for study 2310; NR; not reported, ITT; intention to treat, PP; per protocol

Secondary endpoints included adjusted mean change from baseline to study endpoint in FPG and weight. In study 2309, the adjusted mean change ± standard deviation (sd) from baseline to week 52 in FPG was -0.9 ±0.1mmol/L for vildagliptin and -1.9 ±0.2mmol/L for metformin (p<0.001 versus vildagliptin). The adjusted mean change from baseline to week 52 in body weight was +0.3 ±0.2kg for vildagliptin and -1.9 ±0.3kg for metformin (p<0.001 versus vildagliptin).

In study 2310, the adjusted mean change ±sd from baseline to week 104 in FPG was -0.2 ±0.2mmol/L for vildagliptin and -0.7 ±0.2mmol/L (p<0.025 versus vildagliptin) for gliclazide. The adjusted mean change ±sd from baseline to week 104 in body weight was +0.8 ±0.2kg for vildagliptin and +1.6 ±0.2kg for gliclazide (p<0.01 versus vildagliptin).

In an extension to study 2309, 463 patients (81% of the 569 patients who completed the original study) continued their originally assigned treatment for a further 52 weeks.[3] For patients with a FPG >10mmol/L, pioglitazone could be added to the blinded study drug (as rescue medication) from the first visit of the extension according to the investigator's clinical judgment and prescribing guidelines. In the cohort of patients who entered the extension study, baseline (week 0) HbA1c was 8.4% in the vildagliptin group and 8.8% in the metformin group. The adjusted mean change ±sd in HbA1c from baseline (week 0) to week 104 was -1.0 ±0.1% for vildagliptin and -1.50 ±0.1% for metformin. The between-group difference at week 104 was 0.51 ± 0.1 % (95% CI 0.25 to 0.78*).* Both vildagliptin and metformin monotherapy treatment sustained a clinically meaningful decrease in HbA1c throughout two years of treatment. After two years, there was a significant difference in the adjusted mean change ±sd in body weight from baseline for vildagliptin (+0.5 ±0.4kg) versus metformin (-2.5 ±0.5kg).

A third, double-blind, randomised, multi-centre, active controlled study (study 2327) has been conducted in 786 drug treatment-naïve patients with type 2 diabetes mellitus and HbA1c 7.5% to 11%.[4] Patients were randomised in a 2:1 ratio to vildagliptin 50mg twice daily or rosiglitazone 8mg once daily and the primary endpoint, change from baseline in HbA1c, was assessed at study endpoint (24 weeks) in the intention-to-treat (ITT) population. The adjusted mean change ±sd in HbA1c from baseline to study end point was -1.1 ±0.1% in the vildagliptin group (n=459) and -1.3 ±0.1% in the rosiglitazone group (n=238); 95% CI for between-group difference, -0.01 to 0.39. Non-inferiority was demonstrated if the upper limit of the 95% confidence interval (CI) for the between treatment difference in HbA1c did not exceed 0.4% and therefore non-inferiority was met. The HbA1c reductions in the PP population (-1.20% versus -1.48%) were consistent with those seen in the primary ITT population; however, non-inferiority was not achieved. [7] An 80-week, double-blind and active-controlled extension recruited 598 patients who had completed the 24-week study.[5] At week

104, there were significant reductions in HbA1c from baseline (of 24-week study) for vildagliptin (0.82%) and rosiglitazone (1.44%) and the difference between the arms was significant (in favour of rosiglitazone). Given that the comparator, rosiglitazone, is no longer marketed, this study has limited relevance.

Summary of evidence on comparative safety

In the European Public Assessment Report for the monotherapy extension, the European Medicines Agency (EMA) noted that there were no new safety issues identified during the period safety update reports.[6]

In study 2309, the proportion of patients with any adverse event was 70% (364/519) for vildagliptin and 75% (190/252) for metformin. Any gastrointestinal event was experienced by 22% (113/519) versus 44% (110/252) of patients, respectively, and discontinuations due to adverse events occurred in 4.2% versus 7.1% of patients, mainly driven by discontinuations due to gastrointestinal adverse events (0.8% versus 4.4%, respectively). Mild hypoglycaemia occurred in 0.6% versus 0.4% of patients, respectively, and there were no serious (grade 2) hypoglycaemia events.

In study 2310, there were four reports of grade 1 hypoglycaemia in the vildagliptin group (0.7%) versus 14 (1.7%) in the gliclazide group and no reports of grade 2 hypoglycaemia events.

Summary of clinical effectiveness issues

The submitting company has requested that SMC considers the use of vildagliptin when positioned for use in patients for whom both metformin and sulphonylureas are inappropriate due to contraindications or intolerance. Non-inferiority of vildagliptin versus metformin and gliclazide in the pivotal phase III studies was not demonstrated, although it was demonstrated versus rosiglitazone. However, these studies do not reflect the positioning sought by the submitting company. There are no efficacy data for vildagliptin specifically in patients for whom metformin is contraindicated or not tolerated (licensed indication) or when metformin and sulphonylureas are contraindicated or not tolerated (the company's proposed positioning).

The EMA noted that vildagliptin monotherapy lowers HbA1c and this was consistent across studies. However, because the absolute reduction of HbA1c with vildagliptin was less than with comparators, only the second-line monotherapy indication (in patients intolerant or with contraindications to metformin, including renal impairment) could be approved.[6]

The primary outcome measure used in the studies was the change in HbA1c. HbA1c is the most widely accepted measure of long-term glycaemic control, and lowering HbA1c is associated with a reduction in the risk of microvascular and macrovascular complications 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 7.5% are 48mmol/mol and 58mmol/mol in the new units, with the non-diabetic reference range of 4.0% to 6.0% being 20mmol/mol to 42mmol/mol.

Relevant comparators for the positioning sought by the submitting company are sitagliptin and pioglitazone and there are no direct comparative data versus these treatments at licensed doses. The submitting company provided a network meta-analysis (NMA) using a Bayesian hierarchical model with drug-specific random effects with adjustment for placebo effects, to compare the change from baseline in HbA1c at 24 weeks for vildagliptin (50mg twice daily) versus sitagliptin (100mg once daily).

The evidence synthesis has limitations in terms of internal validity, namely the inclusion of only placebo controlled studies where the justification was not considered to be robust. In addition, only four studies were included in the primary analysis and there were some differences in baseline characteristics (proportion of males and duration of diabetes) between the studies. The NMA has limitations in terms of external validity, as extrapolation to the target population may not be possible because the inclusion criteria did not require that patients were intolerant of metformin or sulphonylureas. Also, comparative efficacy versus pioglitazone is not known.

A Cochrane review of DPP-4 inhibitors for type 2 diabetes mellitus was published in 2008 and included 25 studies of sitagliptin and vildagliptin in monotherapy and combination treatment.[7] Three studies of vildagliptin monotherapy versus another monotherapy treatment were available and included the studies versus metformin and rosiglitazone as well as a study versus pioglitazone in which the dose of vildagliptin was unlicensed (100mg once daily). The difference between vildagliptin and monotherapy-control arms (measured as pooled HbA1c-weighted mean differences) was 0.30% (95% CI: 0.14 to 0.46) in favour of control interventions. Similar results were obtained for the sitagliptin monotherapy meta-analysis. Overall, the authors considered that use of vildagliptin and sitagliptin should be limited to individual patients although they did consider that they had some theoretical advantages over standard therapies.

There are other DPP-4 inhibitors available for treating patients who are intolerant of metformin and sulphonylureas. Vildagliptin is administered twice daily and sitagliptin is administered once daily. There is a requirement for monitoring of liver function tests prior to the initiation of vildagliptin, then every three months for the first year of treatment and periodically thereafter. Clinical experts consulted by SMC considered that these factors would influence treatment choices in practice. They also considered that the population eligible for vildagliptin, with respect to the positioning proposed by the company, is very small.

*Other data were also assessed but remain commercially confidential.**

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis (CMA) comparing vildagliptin versus sitagliptin. A five year time horizon was used.

The submitting company justified the choice of comparator on the basis that, for the treatment of type 2 diabetes mellitus in adults, SMC has previously accepted sitagliptin as monotherapy when both metformin and sulphonylureas are inappropriate due to contraindications or intolerance. SMC was requested to consider vildagliptin as an alternative choice of DPP-4 inhibitor in this restricted position. Clinical experts consulted by SMC advised that there are a number of treatment options available for this patient group, but also confirmed that the choice of comparator is appropriate.

The clinical evidence to support the use of a CMA came primarily from the results of a network meta-analysis (NMA) that showed equivalent patient outcomes for vildagliptin and sitagliptin. The results of the economic evaluation are reliant on the assumption of equivalence, and also that patient outcomes are similar beyond the time period covered by the NMA.

The economic analysis compared the total costs per patient for vildagliptin versus the comparator sitagliptin. Costs included drug costs and also the costs of increased liver function and renal function tests, which are specific requirements within the Summary of Product Characteristics (SPC) for vildagliptin and sitagliptin respectively.

The company estimated that the total cost for vildagliptin is £2,182 versus £2,218 for sitagliptin, representing a saving of £36 over the five year time horizon. Based on medicines cost alone, the annual cost of vildagliptin is less than sitagliptin. However, during the first year of the analysis, the total annual cost for vildagliptin is higher than for sitagliptin – largely due to the increased requirement for liver function tests with vildagliptin. Beyond this first year, the total annual cost for vildagliptin falls below the total annual cost for sitagliptin. At the end of the five year analysis, the higher first-year cost of vildagliptin has been offset and a saving is demonstrated.

Key uncertainties with the economic case related to the external validity of the NMA, specifically the time horizon used within the model, and the number and frequency of liver and renal tests included.

The submitting company provided further analyses to alleviate these concerns, the key results of which are as follows.

- Based on the method of analysis described above, the assumption of a three year time horizon results in a total cost for vildagliptin of £1,329, and a total cost of £1,334 for sitagliptin, representing a saving with vildagliptin of £5 over three years.
- Assuming annual liver and renal function tests for both arms, in addition to the increased monitoring in year one, results in savings with vildagliptin of £18 over three years and £57 over five years.
- Only when patients in the sitagliptin arm are not deemed to receive annual liver function tests are savings not demonstrated with vildagliptin.

Given these results, the economic case was demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline 116; Management of diabetes in March 2010.[8]
The following recommendations are included:

- Metformin should be considered as the first line oral treatment option for overweight patients with type 2 diabetes.
- Sulphonylureas should be considered as first line oral agents in patients who are not overweight, who are intolerant of, or have contraindications to, metformin.
- DPP-4 inhibitors may be used to improve blood glucose control in people with type 2 diabetes.
- Pioglitazone can be added to metformin and sulphonylurea therapy, or substituted for either in cases of intolerance.
- Alpha-glucosidase inhibitors can be used as monotherapy for the treatment of patients with type 2 diabetes if tolerated.

The National Institute for Health and Clinical Excellence (NICE) published clinical guideline 87; Type 2 diabetes: the management of type 2 diabetes in May 2009.[9]
The following recommendations are included:

- Start metformin treatment in a person who is overweight or obese and whose blood glucose is inadequately controlled by lifestyle interventions (nutrition and exercise) alone.

- Metformin should also be considered as a first-line option in people who are not overweight.
- Consider a sulfonylurea as an option for first-line glucose-lowering therapy if:
    - the person is not overweight
    - the person does not tolerate metformin (or it is contraindicated) or
    - a rapid response to therapy is required because of hyperglycaemic symptoms.
- Consider acarbose for a person unable to use other oral glucose-lowering medications.

The guideline does not include any other advice on monotherapy treatment options.

Both guidelines predate the licensing of vildagliptin for monotherapy.

Additional information: comparators

Monotherapy treatment options in type 2 diabetes mellitus are sulphonylureas, sitagliptin, pioglitazone and repaglinide.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Vildagliptin	**50mg twice daily**	**413**
Tolbutamide	500 to 1500mg daily	192 to 576
Sitagliptin	100mg daily	432
Pioglitazone	15 to 45mg daily	142 to 231
Glipizide	2.5 to 20mg daily	39 to 156
Gliclazide	40 to 320mg daily	54 to 55
Repaglinide	1 to 16mg daily	28 to 54
Glimepiride	1 to 4mg daily	14 to 43

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 18 September 2012. All drugs are taken orally and some as divided doses depending on dose.

Additional information: budget impact

The submitting company estimated the population eligible for monotherapy treatment to be 903 in year 1 rising to 1,042 in year five with an estimated uptake rate of 10% in all years. The gross impact on the medicines budget was estimated to be £37k in year 1 and £43k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £36k in year 1 and £42k in year 5.

References

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

1. Schweizer et al. Comparison between vildagliptin and metformin to sustain reductions in HbA(1c) over 1 year in drug-naïve patients with Type 2 diabetes. Diabet Med. 2007 Sep;24(9):955-61

2. Foley JE, Sreenan S. Efficacy and safety comparison between the DPP-4 inhibitor vildagliptin and the sulfonylurea gliclazide after two years of monotherapy in drug-naïve patients with type 2 diabetes. Horm Metab Res. 2009 Dec;41(12):905-9

3. Goke et al. Efficacy and safety of vildagliptin monotherapy during 2-year treatment of drug-naïve patients with type 2 diabetes: comparison with metformin. Horm Metab Res. 2008 Dec;40(12):892-5.

4. Rosenstock J et al. Comparison of vildagliptin and rosiglitazone monotherapy in patients with type 2 diabetes: a 24-week, double-blind, randomized trial. Diabetes care. 2007 Feb;30(2):217-23.

5. Rosenstock J et al. Long-term 2-year safety and efficacy of vildagliptin compared with rosiglitazone in drug-naïve patients with type 2 diabetes mellitus. Diabetes Obes Metab 2009 Jun;11(6):571-8

6. European Medicines Agency. European Public Assessment Report. EMA/CHMP/963014/2011. 15 December 2011. www.emea.europa.eu [accessed on 4 September 2012]

7. Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch C. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetesmellitus. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD006739. DOI: 10.1002/14651858.CD006739.pub2

8. Scottish Intercollegiate Guideline Network. Guideline number 116; Management of diabetes. March 2010. www.sign.ac.uk [accessed on 4 September 2012]

9. National Institute for Health and Clinical Excellence. Clinical guideline 87: The management of type 2 diabetes. March 2009. www.nice.org.uk [accessed on 4 September 2012]

This assessment is based on data submitted by the applicant company up to and including 16 November 2012.

**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. These have been confirmed from the eVadis drug database. 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.