

vildagliptin 50mg tablets (Galvus®)

No. (435/07)

Novartis

7 December 2007 (*Issued March 2008*)

The Scottish Medicines Consortium 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 for the treatment of type 2 diabetes mellitus as dual oral therapy in combination with metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin.

It is restricted to use in patients only when the addition of sulphonylureas is not appropriate, and represents an alternative to other agents such as thiazolidinediones. Efficacy, as assessed by measurement of glycated haemoglobin (HbA_{1c}), is similar to thiazolidinedione drugs added at this stage in therapy. It appears to have minimal effect on body weight.

Vildagliptin is also licensed for use in combination with sulphonylureas or thiazolidinedione drugs for the treatment of type 2 diabetes. The manufacturer's submission related only to the use of vildagliptin in combination with metformin. SMC cannot recommend the use of vildagliptin in combination with these agents.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

The treatment of type 2 diabetes mellitus as dual oral therapy in combination with:

- metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin,
- a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance,
- a thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate.

Dosing information

When used in dual combination with metformin, the recommended daily dose of vildagliptin is 100mg, administered as one dose of 50mg in the morning and one dose of 50mg in the evening.

Product availability date

06 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.

The clinical efficacy of vildagliptin in combination with metformin was assessed in a pivotal study against pioglitazone plus metformin. This study was a 24-week multicentre, double-blind, randomised, active controlled, parallel-group phase III study which recruited patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy alone (with a baseline HbA_{1c} between 7.5% and 11%). An additional 28-week single blind extension phase of the study was undertaken to assess safety. Patients were randomised in a ratio of 1:1 to vildagliptin 50mg twice daily or pioglitazone 30mg daily, both in combination with metformin (continued at the stable dose of at least 1,500mg daily.) No other oral anti-diabetic therapy was permitted during the study and no rescue medication for hyperglycaemia was permitted. Patients with unsatisfactory therapeutic effects had to withdraw from the study. The primary efficacy objective of the study was to demonstrate that the HbA_{1c} reduction from baseline to the week-24 endpoint with vildagliptin 50mg twice daily was non-inferior to that with pioglitazone 30mg daily (using a non-inferiority margin of 0.4% HbA_{1c} in the per protocol population). The secondary efficacy outcomes included change from baseline to endpoint of fasting plasma glucose (FPG, using a non-inferiority margin of 0.6mmol/L) and body weight change. An ANCOVA model was used for analysis and the last observation carried forward (LOCF) approach was used for those patients who did not have a week-24 HbA_{1c} measurement.

Of 576 randomised patients, 510 patients (264 in the vildagliptin group and 246 in the pioglitazone group) were included in the per protocol (PP) population. A total of 506 (88%) patients completed the study (262 in the vildagliptin group and 244 in pioglitazone group). Discontinuation from the study was due mainly to withdrawal of consent (3.6%), adverse events (AEs, 3.0%) and unsatisfactory therapeutic effect (2.8%). The primary objective of the study was met with vildagliptin 50mg twice daily demonstrating 'non-inferiority' to pioglitazone 30mg daily with regard to reduction in HbA_{1c} from baseline (when defined as a margin of

0.4%, equivalent to around 40% of the therapeutic effect). The non-inferiority criterion for the FPG endpoint was not reached after 24 weeks.

Table: ANCOVA results for per protocol (PP) population for change from baseline to week 24

<u>Treatment</u>	<u>n</u>	<u>Baseline mean (SE)</u>	<u>Adjusted mean change (SE)</u>	<u>Mean difference to comparator (SE)</u>	<u>95% Confidence Intervals</u>
HbA_{1c} (%)					
Vildagliptin 50mg twice daily + Metformin	264	8.4 (0.06)	-0.88 (0.05)	0.10 (0.08)*	-0.05 to 0.26*
Pioglitazone 30mg daily + Metformin	246	8.4 (0.06)	-0.98 (0.06)		
FPG (mmol/L)					
Vildagliptin 50mg twice daily + Metformin	264	10.95 (0.16)	-1.35 (0.13)	0.72 (0.19)	0.34 to 1.09
Pioglitazone 30mg daily + Metformin	246	10.98 (0.17)	-2.07 (0.14)		

* indicates non-inferiority to comparator (using 0.4% non-inferiority margin) at one sided 2.5% alpha level.

Summary of evidence on comparative safety

In the pivotal study, vildagliptin (plus metformin) had a similar overall AE profile to pioglitazone (plus metformin) in patients uncontrolled on metformin monotherapy: 2.7% (8/295) of patients in the vildagliptin group and 3.2% (9/281) of patients in the pioglitazone group withdrew due to AEs. The percentage of patients who experienced at least one AE was comparable for vildagliptin (60%, 177/295) and pioglitazone (56%, 158/280). The most common AEs reported by patients in the pivotal study were peripheral oedema (8.8% (26/295) versus 6.1% (17/280) headache (5.4% (16/295) versus 5.0% (14/280), dizziness (4.7% (14/295) versus 2.5% (7/280) and nasopharyngitis (4.1% (12/295) versus 4.6% (13/280) in the vildagliptin and pioglitazone groups, respectively. The higher incidence of oedema in the vildagliptin group was reported as an unexpected finding. The submitting company stated that, as the higher incidence of oedema is inconsistent with that seen in a number of other clinical studies of vildagliptin, further analysis is being conducted in order to identify possible explanations for this apparent discrepancy. In the pivotal study, the frequency of AEs was comparable across primary organ class except for gastrointestinal events that were higher in the vildagliptin group (16%, 47/295) than the pioglitazone group (9%, 25/280). The increase in body weight was significantly less in the vildagliptin group (0.31kg) compared to the pioglitazone group (1.91 kg). Comparative safety data on the long-term use of vildagliptin are not available.

Analysis of pooled data involving around 8,000 patients presented to the EMEA in November 2007 offered some detail around abnormal liver enzyme levels. This resulted in a recommendation not to prescribe vildagliptin to patients with liver impairment and to conduct liver function test monitoring at the start of treatment, every 3 months for the first year and then periodically thereafter.

Summary of clinical effectiveness issues

No head-to-head data comparing vildagliptin and rosiglitazone as add-on therapy to metformin are available. This is important as information from a number of reference sources indicates that rosiglitazone is the most widely prescribed glitazone in Scotland, although the balance might be changing due to concerns over its cardiovascular safety.

Pioglitazone may be given at a higher dose (up to 45mg daily) than the dose used in the pivotal study (30mg daily). Occasional liver function test monitoring is recommended during treatment with either glitazone.

Despite the lack of head-to-head data, the submitting company drew the conclusion that vildagliptin plus metformin has comparable efficacy to rosiglitazone plus metformin by considering their own comparative efficacy data with vildagliptin plus metformin against pioglitazone plus metformin and the results of a number of meta-analyses and systematic reviews that indicate comparability between rosiglitazone and pioglitazone, when given in combination with metformin. Whilst the logic seems reasonable, this is not a true indirect comparison as the data were not formally synthesised. The submitting company also presented supporting data from a monotherapy study against rosiglitazone 8mg daily. However, this study, which is not relevant to the current indication being considered, only just demonstrated non-inferiority at the 0.4% HbA_{1c} margin (equivalent to around 40% less efficacy) and did not demonstrate non-inferiority for the FPG endpoint. There are no comparative studies against other anti-diabetic agents within the DPP-4 inhibitor class. The extension to the pivotal study will provide additional safety data for vildagliptin but there is a need for more efficacy data that consider long-term health outcomes such as the cardiovascular risk / benefit profile for vildagliptin versus active comparator therapy.

Vildagliptin is also licensed for use in combination with sulphonylurea or thiazolidinedione drugs for the treatment of type 2 diabetes. The manufacturer's submission related only to use of vildagliptin in combination with metformin.

Summary of comparative health economic evidence

The manufacturer submitted a cost minimisation analysis (CMA) that compared vildagliptin 100mg per day to either pioglitazone 30mg per day or rosiglitazone 8mg per day in patients unable to tolerate, or with a contraindication to, a combination of metformin and sulphonylurea. CMA is an appropriate choice of analysis when the new treatment has demonstrated equivalent outcomes with the current treatment. In the case of the comparison with pioglitazone, the manufacturer cited the demonstrated non-inferiority of vildagliptin versus pioglitazone in terms of primary outcome as providing the evidence base for comparable efficacy in the CMA. In the case of the comparison with rosiglitazone, evidence of comparable efficacy was derived from an indirect comparison. Both pieces of analysis focused only on the drug acquisition costs associated with each treatment and looked at the costs over a one year period. The results of the analysis indicated that vildagliptin would be preferred on cost- minimisation grounds to both pioglitazone and rosiglitazone.

Several points should be noted in terms of the analysis that was provided. In the comparison with pioglitazone, the clinical trial found that vildagliptin was non-inferior in terms of the primary outcome measure (using a non-inferiority margin of 0.4% HbA_{1c}) but not in terms of a secondary outcome measure so this implies that vildagliptin may not be comparable in terms of all outcomes. However, as a counterbalance, vildagliptin was associated with a benefit in terms of weight gain and this was not accounted for in the analysis. In terms of the

comparison with rosiglitazone, the analysis used the maximum daily dose of rosiglitazone, which is not used in the majority of patients in clinical practice in Scotland.

The use of lower daily doses of rosiglitazone would erode some of the cost advantage of vildagliptin over rosiglitazone. However, adjusting for this did not alter the conclusions of the analysis. In addition, information for the comparison with rosiglitazone came from an indirect comparison which did not involve a statistical synthesis of the data. Both pieces of analysis only looked at costs over a one year period and implicitly assumed that any difference in effect seen at the end of the 24-week trial period was maintained at one year. There are limited data available at present to support this assumption. The economic analysis did not take into account the levels of liver function testing for vildagliptin patients recommended by the EMEA in November 2007, which may have introduced a small bias in the drug's favour (costs of recommended liver function test monitoring for recipients of the comparator were also not included).

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

Scottish Intercollegiate Guideline Network (SIGN) guideline for the management of diabetes mellitus (SIGN 55), published in November 2001 (currently under review).

National Institute for Health and Clinical Excellence (NICE) guidelines on managing type 2 diabetes mellitus, including the management of blood glucose levels, blood pressure and blood lipids, renal disease and retinopathy (2002). The guideline is currently being updated, with a planned publication date of March 2008.

NICE Technology Appraisal 63 on the use of glitazones in type 2 diabetes mellitus (2003).

Additional information: previous SMC advice

Following an abbreviated submission in March 2004, rosiglitazone, metformin (Avandamet®) was accepted for use within NHS Scotland for the treatment of type 2 diabetes mellitus. It is used for overweight patients who are unable to achieve sufficient glycaemic control at their maximally tolerated doses of oral metformin alone and cannot be treated with a sulphonylurea in combination with metformin.

Following an abbreviated submission in December 2004, a new formulation of Avandamet® was accepted for use in NHS Scotland for the treatment of type 2 diabetes mellitus in patients for whom a combination of rosiglitazone and metformin is appropriate.

Following an abbreviated submission in September 2006, pioglitazone 15mg / metformin 850mg hydrochloride (Competact®) was accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus. It should be used for overweight patients who are unable to achieve sufficient glycaemic control at their maximally tolerated doses of oral metformin alone. It is restricted to patients who cannot be treated with a sulphonylurea in combination with metformin.

Following a full submission in June 2007, exenatide (Byetta®) was accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus in combination with metformin and / or sulphonylureas in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies. It has shown non-inferiority to two insulin regimens with which it has been compared and has a beneficial effect on weight. It is restricted to use as an alternative to insulin in patients who have failed treatment on metformin and / or sulphonylureas and in whom insulin would be the next treatment option.

Following a full submission in September 2007, sitagliptin (Januvia®) was accepted for restricted use within NHS Scotland for treatment of patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin when diet and exercise, plus metformin, do not provide adequate glycaemic control. It is restricted to use in patients only when the addition of sulphonylureas is not appropriate, and represents an alternative to other agents such as thiazolidinediones. Efficacy, as assessed by measurement of HbA_{1c}, is similar to sulphonylurea and thiazolidinedione drugs added at this stage in therapy. It appears to have minimal effects on body weight.

SMC has also considered rosiglitazone (August 2004) and pioglitazone (September 2005) monotherapy, rosiglitazone (June 2005) and pioglitazone (March 2007) triple therapy in combination with metformin and a sulphonylurea and Avandamet (July 2006) in combination with a sulphonylurea as triple therapy for type 2 diabetes mellitus. These indications are not directly related to the indication within the current submission.

Additional information: comparators

Comparators include all other oral antidiabetic agents that can be used in combination therapy with metformin. The main comparators are thiazolidinediones (rosiglitazone and pioglitazone), sulphonylureas and sitagliptin.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
Vildagliptin	50mg twice daily	413^a
Exenatide	5 to 10 micrograms twice daily	828
Rosiglitazone	4 to 8mg once daily	322 to 660
Pioglitazone	15 to 45mg once daily	314 to 480
Sitagliptin	100mg once daily	432
Gliquidone	15mg once daily to 60mg three times daily	32 to 383 ^b
Repaglinide	0.5mg three times daily to 4mg four times daily	143 to 381
Nateglinide	60 to 180mg three times daily	295 to 336
Acarbose	50mg once daily to 200mg three times daily	27 to 304
Gliclazide MR	30 to 120mg once daily	40 to 160
Glimepiride	1 to 4mg once daily	45 to 129
Tolbutamide	500 to 2000mg daily in divided doses	30 to 119
Gliclazide	40mg once daily to 160mg twice daily	12 to 94
Glipizide	2.5mg once daily to 10mg twice daily	19 to 66
Glibenclamide	5 to 15mg once daily	18 to 54

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 5th September 2007, unless otherwise stated. The above costs exclude the cost of metformin when drugs are used in combination. Metformin costs approximately £30 a year at a dose of 1,500mg per day. a)

Cost of vildagliptin supplied by manufacturer as 'commercial-in-confidence' on 19th February 2008. b) Cost of gliquidone obtained from the 53rd edition of the British National Formulary (BNF).

Additional information: budget impact

The manufacturer estimated that the gross drug budget cost of vildagliptin, used as dual oral therapy in combination with metformin, would be £110k in year one rising to £432k in year five. After taking into account the cost that would arise if patients were treated with glitazones, the net drug budget impact would be a saving of £40k in year one rising to a saving of £157k in year five.

The estimates assumed that 2,659 patients would be eligible for treatment in year one rising to 3,482 by year five. Of these eligible patients, it was assumed that 10% would be treated with vildagliptin in year one rising to 30% by year five. It was also assumed that vildagliptin would displace treatment with a comparator drug given at the maximum daily dose. Clinical experts suggest that the majority of patients are not on the maximum daily dose of comparator drug so any savings are likely to be less than those estimated.

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 03 March 2008.

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.