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. (875/13)

Novartis Europharm Limited

08 November 2013

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

vildagliptin (Galvus®) is accepted for restricted use within NHS Scotland.

Indication under review: Treatment of type 2 diabetes mellitus in adults as triple oral therapy in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

SMC restriction: as an alternative dipeptidyl peptidase-4 inhibitor option.

Treatment with vildagliptin reduces HbA1c levels significantly more than placebo when used in combination with metformin and a sulphonylurea. A Bayesian network meta-analysis suggested similar efficacy to another dipeptidyl peptidase-4 inhibitor.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of type 2 diabetes mellitus in adults as triple oral therapy in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

Dosing Information

The recommended daily dose is 100mg, administered as one dose of 50mg in the morning and one dose of 50mg in the evening. When used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia.

Doses higher than 100mg are not recommended.

In patients with moderate or severe renal impairment or with end-stage renal disease, the recommended dose is 50 mg once daily.

Product availability date

September 2012

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. Vildagliptin 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.

SMC has previously accepted vildagliptin for use in combination with a sulphonylurea, and for restricted use as monotherapy or as dual therapy in combination with metformin. The submission under review is for an extension to the marketing authorisation for vildagliptin to include use as triple therapy in combination with metformin and a sulphonylurea. The submitting company has requested that SMC considers the use of vildagliptin as an alternative DPP-4 inhibitor option for this indication.

A multi-centre, randomised, double-blind, phase III study provides evidence for the use of vildagliptin as triple therapy in combination with metformin and a sulphonylurea.[1,2] The study recruited adults (aged 18 to 80 years) with type 2 diabetes and body mass index of 22 to 45kg/m^2. Patients were inadequately controlled on either; metformin monotherapy (≥1,500mg/day: glycosylated haemoglobin [HbA1c] ≥8.5% and ≤11%); or dual therapy, metformin (≥1,500mg/day) in combination with sulphonylurea, “glinide” secretagogues or thiazolidinedione (HbA1c ≥7.5% and ≤11%). Patients underwent a titration and stabilisation phase (up to 3 months), in which the standard background oral anti-diabetic regimen of metformin (≥1,500mg/day) and glimepiride (≥4mg/day) was established. Patients were then considered eligible if HbA1c was between ≥7.5% and ≤11% and were randomised to either vildagliptin 50mg twice daily (n=158) or placebo (n=160) for a 24-week double-blind treatment period. During this period, the metformin dose remained stable and the glimepiride dose could

be reduced only once to a maximum tolerated dose (≥2mg/day) to minimise hypoglycaemia adverse events. Rescue treatment with either insulin or pioglitazone was permitted after six weeks, and was indicated by either symptoms of hyperglycaemia or repeated elevated fasting plasma glucose levels.

The primary outcome was the change in HbA1c from baseline to study endpoint (week 24), analysed in the full analysis set (FAS) using an analysis of co-variance model with imputation of missing data by last observation carried forward. Patients requiring rescue treatment had subsequent efficacy measurements marked as missing. The FAS was defined as all randomised patients who had taken at least one dose of study medication and had at least one post-baseline measurement.[1,2]

Results of the primary outcome and supportive secondary outcomes (HbA1c responder, change in fasting plasma glucose) are presented in the table below.

Outcomes to 24 weeks		Vildagliptin (n=152)	Placebo (n=160)	Treatment difference
Baseline HbA1c, % (SE)		8.75 (0.07)	8.80 (0.07)	
Primary Outcome				
Mean change in HbA1c, % (SE)		-1.01 (0.09)	-0.25 (0.09)	-0.76% (95% CI: -0.98 to -0.53) p<0.001
Secondary Outcomes				
Proportion of responders (achieving target HbA1c)	HbA1c <7.0%	28%	5.6%	p<0.001
	HbA1c ≤6.5%	13%	1.3%	p<0.001
Change in mean fasting plasma glucose (mmol/L)		-1.11	0.02	-1.13 (95% CI: -1.65 to -0.60) p<0.001

Table: Efficacy outcomes for pivotal study analysed in the FAS. SE = standard error, CI= confidence interval.[1]

Fewer patients in the vildagliptin group required rescue medication (3.8% [6/158]) compared with placebo (14% [22/160]). The mean exposure to rescue medication was 8.9 weeks and 10.4 weeks in the vildagliptin and placebo groups, respectively.[1]

No assessment of quality of life was conducted.

Summary of evidence on comparative safety

No comparative safety data are available. Refer to the summary of product characteristics for details of adverse effects. During the pivotal study there were no new safety concerns.

Similar proportions of patients in each group reported adverse events during the pivotal study: 50% (79/157) and 48% (76/160) of patients in the vildagliptin and placebo groups, respectively. One patient in each group discontinued the study due to adverse events. In total, four patients required a glimepiride dose reduction: vildagliptin, n=3, and placebo, n=1.

The incidence of drug-related adverse events was greater in the vildagliptin group (13%) compared with the placebo group (4.4%). The reported drug-related adverse events for the

vildagliptin group compared with placebo included: dizziness (3.8% versus 0%), tremor (3.2% versus 0%), hypoglycaemia (2.5% versus 0.6%), and skin and subcutaneous tissue disorders such as hyperhidrosis and pruritis (3.8% versus 0.6%).

There was only one incident of major hypoglycaemia which occurred post-surgery in a patient in the vildagliptin group who was unable to initiate self-treatment and had a plasma glucose measurement <3.1mmol/L.

The European Medicines Agency (EMA) considered vildagliptin to have a neutral effect on body weight. The change in mean body weight was 0.6kg in the vildagliptin group compared with -0.1kg in the placebo group.[1]

Summary of clinical effectiveness issues

The submitting company has requested that SMC considers the use of vildagliptin as an alternative DPP-4 inhibitor option for the treatment of type 2 diabetes mellitus in adults as triple oral therapy in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control. Vildagliptin is one of four DPP-4 inhibitors licensed for use as triple oral therapy with metformin and a sulphonylurea in patients with type 2 diabetes. Linagliptin, sitagliptin and saxagliptin have been accepted for use in this indication by SMC. 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.

In the placebo-controlled, randomised, double-blind study, the addition of vildagliptin treatment to metformin and a sulphonylurea was associated with a clinically significant reduction in HbA1c after 24 weeks compared with placebo. Secondary outcomes supported the findings of superiority of vildagliptin, with higher proportions of responders (achieving target HbA1c levels) and reduced fasting plasma glucose levels, compared with placebo.[1,2] HbA1c is a surrogate measure of glycaemic control and data are currently limited to 24 weeks. 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.[3,4] 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.

There are limitations of the evidence in terms of generalisability to the Scottish population. The study population tended to be younger, with a mean age of 55.1 years, than the population with type 2 diabetes in Scotland. The reported median age of people with type 2 diabetes in Scotland is 65 to 69 years.[1,2,5] The study population was predominantly of Asian ethnicity, with approximately 22 to 24% of patients of Caucasian background. However, this concern is attenuated by sub-group analysis which revealed a similar magnitude of treatment effect between the races and for the overall population.

There are no direct comparative data versus other DPP-4 inhibitors as part of triple oral therapy. To support the economic case, the submitting company presented a Bayesian network meta-analysis (NMA) in which vildagliptin was compared with sitagliptin using placebo as a common comparator. The network was comprised of two similarly designed randomised, double-blind, controlled studies in adults with type 2 diabetes mellitus given triple oral anti-diabetic treatment

(DPP-4 inhibitor/placebo with metformin and sulphonylurea).[2,6] Several efficacy outcomes were compared: change after 24 weeks of treatment in HbA1c, fasting plasma glucose and body weight. The results of the primary analysis suggest that vildagliptin has similar efficacy to sitagliptin for these outcomes.

Sensitivity analyses were presented which supported the primary analysis: an adjusted pairwise comparison using the Bucher method and a matching-adjusted indirect comparison (MAIC). The MAIC attempted to address the identified differences between the studies' populations that potentially biased the primary analysis (e.g. distribution of racial background, baseline HbA1c, body-mass index and body weight).

A limitation of note was that there was no comparison of safety outcomes. Furthermore, although both studies reported HbA1c responder rates at the 7.0% threshold, this outcome was not compared in the indirect comparison analyses.

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

Summary of comparative health economic evidence

The company submitted a simple cost-minimisation analysis over a 7-year time horizon comparing vildagliptin to sitagliptin for use as triple therapy in adult patients with type 2 diabetes mellitus when diet and exercise plus dual therapy do not provide adequate glycaemic control. The submitting company has therefore requested that SMC considers vildagliptin as an alternative DPP-4 inhibitor option. Clinical experts have confirmed that sitagliptin is an appropriate comparator.

The clinical evidence to support the cost-minimisation analysis came from the results of a NMA, which demonstrated comparable efficacy for vildagliptin and sitagliptin. The network was comprised of two randomised, double-blind, controlled studies in adults with type 2 diabetes mellitus given triple oral anti-diabetic treatment. The results of the economic evaluation are reliant upon the conclusion of comparable efficacy from the NMA, and also that patient outcomes remain comparable beyond the duration covered by the NMA.

The economic analysis compared the total costs per patient for vildagliptin versus the comparator, sitagliptin. Acquisition costs of both medicines were included as well as additional liver functioning tests (LFTs) required for patients using vildagliptin. The submitting company presented two scenarios regarding the number of LFTs conducted in each year. In the first scenario, vildagliptin achieved marginal cost savings versus sitagliptin over the 7-year duration of the model (£3,034.36 versus £3,034.99 respectively). Despite lower annual drug acquisition costs (£414.01 versus £433.57), vildagliptin was associated with a higher total annual cost due to 5 additional LFTs in year 1 followed by 1 test per year for subsequent years. At the end of the 7 year analysis, the higher first-year cost of vildagliptin was offset and a saving had been demonstrated.

The second scenario assumed that LFTs would be performed annually in all patients on triple therapy, regardless of which DPP-4 is used. Vildagliptin was associated with four additional LFTs in year 1 and none in subsequent years, and demonstrated cost savings versus sitagliptin by year 3 of treatment (total annual costs: £1,291.59 versus £1,300.71).

The following limitations were noted with the analysis:

- It may not be appropriate to base the analysis on the first scenario because of the length of time horizon - patients are unlikely to remain on treatment for this period of time. In this scenario, vildagliptin only becomes cost-saving after 7 years because of the number of LFTs.
- The cost-minimisation analysis was based on an indirect comparison for which some weaknesses were noted.

Despite these weaknesses, the economic case has 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.[3] 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 third-line treatment of type 2 diabetes mellitus to be added in combination with metformin and sulfonylurea; additional oral anti-diabetic drugs, pioglitazone or DPP-4 inhibitors; or injections of GLP-1 analogues or commencement of insulin. Third-line treatment should be continued if individualised target 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.[4] Recommendations consider 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.[7] 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 other DPP-4 inhibitors (linagliptin, saxagliptin and sitagliptin) are licensed for use as triple oral therapy in combination with metformin and a sulphonylurea when this regimen alone with diet and exercise does not provide adequate glycaemic control.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Vildagliptin	**50mg orally twice daily**	**413**
Linagliptin	5mg orally once daily	432
Sitagliptin	100mg orally once daily	432
Saxagliptin	5mg orally once daily	411

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 21 August 2013.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 196 in year 1 and 1,048 in year 5, with an estimated uptake rate of 3.3% in year 1 and 6.15% in year 5. The gross impact on the medicines budget was estimated to be £205k in year 1 and £434k in year 5. As sitagliptin was the DPP-4 inhibitor expected to be displaced, the net medicines budget impact was estimated to be savings of £10k in year 1 and £20k in year 5.

References

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

1) European Medicines Agency. Assessment report: EMA/CHMP/568007/2012. 20 Sep 2012. Available at www.ema.europa.eu
2) *Commercial In Confidence**
3) Scottish Intercollegiate Guidelines Network. Management of diabetes: A national clinical guideline. March 2010; Publication No 116 (SIGN 116).
4) National Institute for Health and Care Excellence. Type 2 diabetes: management of type 2 diabetes (clinical guideline 87), 2009.
5) NHS Scotland. Scottish Diabetes Survey. 2011. Available at: http://www.diabetesinscotland.org.uk/Publications/SDS_2011.pdf [Accessed 19 August 2013].
6) Hermansen K, Kipnes M, Luo E et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. Diabetes, Obesity and Metabolism 2007; 9: 733-45.
7) Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycaemia in type 2 diabetes: a patient-centred approach. Diabetes Care 2012;35:1364-79.

This assessment is based on data submitted by the applicant company up to and including 11 October 2013.

**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.