All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Vildagliptin (Galvus®)
50 mg tablets

Reference number: 1531

FULL SUBMISSION

This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

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AWMSG Secretariat Assessment Report
Vildagliptin (Galvus®) 50 mg tablets

This assessment report is based on evidence submitted by Novartis Pharmaceuticals UK Ltd on 19 November 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Vildagliptin (Galvus®) is indicated in the treatment of type 2 diabetes mellitus as monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance[1].
Dosing	When used as monotherapy, the recommended daily dose of vildagliptin is 100 mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening[2].
Marketing authorisation date	30 January 2012 for the indication under consideration (first licensed for the treatment of type 2 diabetes mellitus on 26 September 2007)[2,3].

2.0 DECISION CONTEXT

2.1 Background

In 2011, diabetes mellitus affected 160,533 patients in Wales[4] and approximately 85% of these patients have type 2 diabetes mellitus (T2DM)[5]. T2DM is caused by insufficient insulin production by pancreas beta-cells, or the inability of the body to properly utilise endogenous insulin[5]. T2DM is associated with increased cardiovascular risk and microvascular complications such as eye, nerve, and renal damage[6].

In T2DM patients with glycosylated haemoglobin (HbA1c) levels ≥ 6.5%, the National Institute of Health and Clinical Excellence (NICE) Clinical Guideline (CG) 87 recommends first-line treatment with metformin. Where metformin is not tolerated or is contraindicated, the use of sulphonylureas may be considered[1,6]. NICE CG87 suggests adding a dipeptidyl peptidase (DPP-4) inhibitor (sitagliptin, vildagliptin) to a first-line therapy (metformin or sulphonylurea) when control of blood glucose remains or becomes inadequate[6]. Vildagliptin is a DPP-4 inhibitor which acts by increasing the levels of active incretin hormones, therefore resulting in an increase in insulin secretion levels and a reduction in glycaemia[2]. The company estimates that approximately 11,453 patients would be eligible for vildagliptin treatment in Wales[1].

The company suggest that in patients for whom the NICE-recommended first-line therapies (metformin or sulphonylurea) are either contraindicated (e.g. in renal impairment) or not tolerated, vildagliptin may be considered as an alternative second-line therapy[1].

2.2 Comparators

The comparator requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) was sitagliptin (Januvia®▼).

2.3 Guidance and related advice

- NICE. Type 2 diabetes: the management of type 2 diabetes. Clinical guideline 87 (2009)[6].

- Scottish Intercollegiate Guidelines Network. Management of diabetes. Guideline 116 (2010)[7].

The All Wales Medicines Strategy Group (AWMSG) has previously issued the following recommendations:

- Vildagliptin (Galvus®) 50 mg tablets are recommended as an option for use within NHS Wales for the treatment of type 2 diabetes in patients with moderate or severe renal impairment (2012)[8].
- Sitagliptin (Januvia®▼) 25 and 50 mg tablets are recommended as an option for use within NHS Wales for the improvement of glycaemic control in type 2 diabetes mellitus patients with moderate renal impairment (CrCl ≥ 30 to < 50 ml/min), severe renal impairment (CrCl < 30 ml/min) or with end-stage renal disease (ESRD) requiring haemodialysis or peritoneal dialysis (2012)[9].
- Saxagliptin (Onglyza®▼) is recommended as an option for use within NHS Wales for the treatment of adult patients aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control in combination with insulin (with or without metformin) when this regimen alone with diet and exercise does not provide adequate glycaemic control (2012)[10].
- Linagliptin (Trajenta®▼) is not recommended for use within NHS Wales for the treatment of type 2 diabetes mellitus to improve glycaemic control (2012)[11].
- Saxagliptin (Onglyza®▼) is recommended as an option for use within NHS Wales as an add-on combination therapy for use in adult patients with type 2 diabetes mellitus with moderate or severe renal impairment to improve glycaemic control (2011)[12].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

Due to a lack of direct evidence, the company submission includes a network meta-analysis, which provides an indirect comparison of the efficacy of vildagliptin monotherapy versus sitagliptin monotherapy. The company have also provided information on five active comparator studies comparing vildagliptin with metformin, gliclazide, rosiglitazone (marketing authorisation suspended) and placebo. However, owing to the indication under appraisal, and recommendations from NICE CG87 regarding vildagliptin's place in therapy, the active comparator studies will not be included in this section.

3.1 Indirect analysis of vildagliptin versus sitagliptin

The company submission includes a network meta-analysis to determine the HbA1c reduction in T2DM patients using vildagliptin 50 mg twice daily and sitagliptin 100 mg once daily at 24-weeks (primary analyses) and at 12-weeks (secondary analyses).

The 24-week primary analyses comprised of four multinational, double-blind, randomised, placebo-controlled studies two of which had a vildagliptin arm and two which had a sitagliptin arm. T2DM patients (n = 1,164); with HbA1c levels of between 7 and 11% received vildagliptin 50 mg twice daily (n = 169) and sitagliptin 100 mg once daily (n = 404). The placebo-adjusted model showed that there was no significant difference in the change in HbA1c (results are commercial in confidence) between vildagliptin 50 mg twice daily and sitagliptin 100 mg once daily. Results of the change in HbA1c, for the individual trials, are shown in Table 1.

The 12-week secondary analyses consisted of 11 studies in total; seven of which were multinational, double-blind, randomised placebo-controlled studies. The remaining four were restricted to Japan and due to population differences, these studies will not be discussed further. Results for secondary analysis are commercial in confidence.

Table 1. Mean change from baseline in HbA1c levels at 24-weeks

	Vildagliptin 50 mg	Placebo	Sitagliptin 100 mg	Placebo
Study	**Change in HbA1c from baseline at 24 weeks (%)**			
Dejager[13]	−0.8	−0.3	–	–
Pi-Sunyer[14]	−0.7	0.0	–	–
Aschner[15]	–	–	−0.61	0.18
Goldstein[16]	–	–	−0.66	0.17
Vildagliptin was administered twice daily whereas, sitagliptin was administered once daily				

3.2 Evidence of comparative safety

In the trials involving vildagliptin, the majority of adverse events (AEs) were considered to be mild to moderate[13,14]. Upper respiratory tract infection, dizziness, hypertension, headache and nasopharyngitis were reported as frequently found AEs (> 5% of the treatment group). No relevant differences were observed for any commonly reported AEs between the vildagliptin and placebo treatment groups[13,14].

3.3 AWTTC critique

- The indirect comparison[1] between vildagliptin and sitagliptin may have cross-trial differences in patient populations, and although adjustments were made for HbA1c data, unobserved cross-trial differences cannot be ruled out.
- The European Public Assessment Report states that the reduction in HbA1c was found to be clinically relevant in trials using vildagliptin 50 mg twice daily[17].
- The study population used within the network meta-analysis[1] was not restricted to patients intolerant to metformin and therefore, may not be truly representative of the population of patients expected to receive vildagliptin monotherapy, as outlined in NICE CG87 and the licensed indication[2,6].
- The studies included in the company submission demonstrate outcomes for 12 and 24 weeks; primary analyses were conducted at 24-weeks[1]. No long-term information on the efficacy of vildagliptin monotherapy versus sitagliptin monotherapy was provided.
- The company submission included a secondary analysis at 12 weeks, however the 12-week data was not reported in the individual published trials and the company have stated that where change in Hb1Ac was not available, values were estimated or calculated from mean levels reported at baseline and endpoints[1].
- Vildagliptin should not be used in patients with hepatic impairment and liver function tests should be performed prior to the initiation of treatment with vildagliptin in order to measure the patient's baseline value. Liver function should be monitored during treatment with vildagliptin at three-month intervals during the first year and periodically thereafter[2]. Sitagliptin can be used in patients with mild to moderate hepatic impairment and routine liver function monitoring is not necessary with sitagliptin treatment[18].
- When used in patients without moderate or severe renal impairment, vildagliptin is administered twice daily[2] whereas sitagliptin is administered once daily[18]. This could potentially influence adherence and patient preferences.
- There is no experience of vildagliptin use in clinical trials in patients with a New York Heart Association (NYHA) functional class III-IV and therefore use in these patients is not recommended[2].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission[1] describes a cost-minimisation analysis of vildagliptin 50 mg twice daily versus sitagliptin 100 mg once daily as a monotherapy for the treatment of type 2 diabetes in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance. The company anticipate that vildagliptin will be used as a second-line therapy in patients for whom NICE-recommended first-line monotherapy (metformin or sulphonylurea) is either contraindicated (e.g. renal impairment) or not tolerated. The analysis is based on the assumption of equivalence in efficacy of vildagliptin 50 mg twice daily versus sitagliptin 100 mg once daily derived from adjusted indirect comparisons of published studies comparing sitagliptin with placebo and vildagliptin with placebo at 12 and 24 weeks. The analysis assumes no difference in medicine administration and service costs other than liver function monitoring costs for vildagliptin and renal function test costs for sitagliptin. The company adopted a five-year time horizon which takes into account less intensive liver and renal function monitoring beyond year one.

4.1.2 Results

Results of the base case analysis of vildagliptin 50 mg twice daily versus sitagliptin 100 mg once daily for the treatment of type 2 diabetes are summarised in Table 2. Treatment with vildagliptin was estimated to be more costly compared to treatment with sitagliptin in the first year, but less costly than sitagliptin in following years. The difference in total costs during year one was driven by more intensive liver function testing in patients receiving vildagliptin. Beyond year one, the difference in total costs was driven by lower acquisition costs for vildagliptin. Over a period of five years treatment with vildagliptin was marginally less costly compared to treatment with sitagliptin.

Table 2. Company-reported results of the base case cost-minimisation analysis.

Base case	Vildagliptin 50 mg twice daily	Sitagliptin 100 mg once daily	Difference (calculated by AWTTC)
Annual medicine acquisition costs	£414.01	£433.57	-£19.56
Monitoring costs during first year*	£56.50	£15.28	£41.22
Total cost over first year	£470.51	£448.85	£21.66
Annual monitoring costs beyond year one*	£11.30	£7.64	£3.66
Annual total cost beyond year one	£425.31	£441.21	-£15.90
Total cost over first 5 years	**£2,171.75**	**£2,213.69**	**-£41.94**
*Monitoring costs refer to liver and renal function tests, as specified in the relevant SPCs[2,18]			

The company conducted sensitivity analyses assuming annual discount rates of 3.5% and 6% for both vildagliptin and sitagliptin treatments beyond year one. The difference in total costs between the two treatments was £36.73 for the 3.5% discount rate and £33.42 for the 6% discount rate. The company acknowledged that patients with moderate to severe renal impairment may require a reduction in the dosage of both vildagliptin and sitagliptin. This will result in a reduction of the acquisition costs for vildagliptin, but not for sitagliptin, which has the same acquisition costs regardless of tablet strength.

4.1.3 AWTTC critique

It is unclear whether or not the cost savings from the use of vildagliptin instead of sitagliptin, as estimated by the company, would be realised in practice. Evidence for equivalence is limited to indirect comparisons of HbA1c effects in short term placebo-controlled trial data. Taking into account the associated liver and renal function tests, monotherapy using vildagliptin twice daily is only cost saving compared with sitagliptin when used continuously over periods exceeding one year, and many patients may not achieve HbA1c targets using monotherapy over an extended period of five years, as is suggested by the company. Periodic renal function monitoring is recommended in all patients[6], irrespective of treatment received, but appear to be excluded from the company's costings of vildagliptin monotherapy. Under an assumption of equivalence, there would appear be little difference in costs between vildagliptin 50 mg twice daily and sitagliptin 100 mg once daily when used as monotherapy.

Strengths of the economic evidence include:

- In the absence of direct comparative data for vildagliptin and sitagliptin, a systematic literature review was undertaken to identify studies for inclusion in an indirect network meta-analysis to assess the therapeutic equivalence of vildagliptin and sitagliptin.

Limitations of the economic evidence include:

- The cost-minimisation analysis presented by the company is based on the assumption of equal efficacy of vildagliptin 50 mg twice daily and sitagliptin 100 mg once daily, based on an indirect comparison of short-term (12 and 24 weeks), placebo-controlled studies. The company acknowledged differences in patient populations between studies used in the meta-analysis (e.g. duration of diabetes), which may confound results.
- Data from trials comparing metformin as a common comparator were excluded from the analysis on the basis that vildagliptin is licensed for use where metformin is not tolerated or appropriate. However, none of the trials included in the

company's submission in support of vildagliptin or sitagliptin efficacy as monotherapy were conducted in such a patient population.

- Cost minimisation analyses implicitly assume therapeutic equivalence in all aspects of health outcomes; however, vildagliptin and sitagliptin have different requirements for liver and renal function monitoring, suggesting potential for differences in the safety profiles of these medicines. In addition, when used in patients without moderate or severe renal impairment, vildagliptin is administered twice daily whereas sitagliptin is administered once daily. This could potentially influence adherence and patient preferences. Vildagliptin at a dose of 50 mg once daily is currently recommended as an option for use within NHS Wales for the treatment of type 2 diabetes in patients with moderate or severe renal impairment[8].
- Periodic renal function tests are recommended in all patients with type 2 diabetes mellitus[6], but the costs of renal function monitoring have been excluded from the overall costs of vildagliptin. It is therefore possible that the company has overestimated the cost savings anticipated from the use of vildagliptin monotherapy instead of sitagliptin. Under an assumption of therapeutic equivalence, actual cost differences are likely to be small.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on diabetes prevalence figures for Wales (2011)[19] and the average mortality rate due to diabetes in Wales (2001-2009)[20], the company estimated that there will be 174,269 people with diabetes in Wales in 2012, rising to 209,307 in five years. Using market research data, the company estimated that there were approximately 114,856 people treated for type 2 diabetes in 2011 in Wales, of which 522 received DPP-4 inhibitor monotherapy. The market share of DPP-4 inhibitors is anticipated to remain static, but the number of patients who will be treated with DPP-4 inhibitors is expected to rise from 543 in 2012 to 652 in 2017 due to increasing incidence of diabetes. Given that 7.3% of patients currently treated with DPP-4 inhibitor monotherapy already receive vildagliptin, the company anticipates that an additional 2.7% of patients will switch to vildagliptin from other DPP-4 inhibitors, resulting in a 10% market share. The number of patients receiving vildagliptin monotherapy in Wales is expected to be 57 in year one, rising to 65 in year five.

5.1.2 Results of company's budget impact analysis

The company-reported numbers of patients eligible for treatment with vildagliptin and the associated costs over the five year period are summarised in Table 3. According to company estimates, the total cost of treatment of patients with vildagliptin (including monitoring) will be £26,819 in year one rising to £27,736 in year five (£132,659 over the period of five years). Scenario analyses were conducted by the company to estimate costs associated with anticipated switches of 10% to 50% of patients from sitagliptin to vildagliptin. Over the entire five year period 2012-16, the company's estimates indicate cumulative cost savings ranging from £1,861 (for 10% switch), to £9,390 (for 50% switch). These estimates consist of additional costs in the first year of £953 (for 10% switch) to £4,817 (for 50% switch), with cost savings in subsequent years.

Table 3. Company-reported costs associated with use of vildagliptin (Galvus®) for the treatment of type 2 diabetes as monotherapy

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	565	586	608	630	652
Uptake	10%	10%	10%	10%	10%
Number of treated patients	57	59	61	63	65
Vildagliptin acquisition costs	£23,599	£24,427	£25,255	£26,083	£26,911
Vildagliptin monitoring costs	£3,221	£757	£780	£802	£825
Total cost	**£26,819**	**£25,184**	**£26,035**	**£26,885**	**£27,736**

5.1.3 AWTTC critique of the budget impact analysis

- The company has made efforts to estimate eligible patient numbers using a wide range of sources, although this would be associated with a degree of uncertainty in uptake in practice.
- The actual cost estimates associated with vildagliptin and sitagliptin are based on those in the company's cost minimisation analysis (see Section 4). The uncertainties and limitations outlined above in Section 4 would therefore apply to the company's budget impact analysis. It is therefore possible that the company has overestimated the cost savings anticipated from the use of vildagliptin monotherapy instead of sitagliptin.
- Collectively, the budget impact estimates are subject to uncertainty and it is not clear that the anticipated cost savings over the long term would be realised in practice.

5.2 Comparative unit costs

Vildagliptin is licensed for use as monotherapy in type 2 diabetes mellitus where metformin is not approriate[2]. However, the company anticipates vildagliptin to be used as a second-line therapy in patients for whom NICE-recommended first-line monotherapy using metformin or sulphonylurea is either contraindicated (e.g. renal impairment) or not tolerated. Table 4 provides comparative acquisition costs for vildagliptin and other medicines with licensed indications that overlap the vildagliptin licensed indication. See the relevant SPCs[2,18,21–27] and NICE CG87 for the management of type 2 diabetes[6] for dosing details and recommendations for use.

Table 4. Examples of medicine acquisition costs for the treatment of type 2 diabetes as monotherapy.

Treatment	Example regimen	Annual cost of treatment
Examples of sulphonylureas		
Gliclazide (non-proprietary)	80 mg–320 mg daily (in divided doses)	£9 –£36
Glimepiride (non-proprietary)	2 mg–4 mg daily	£15– £18
Tolbutamide (non-proprietary)	500 mg –1,500 mg daily (in divided doses)	£29– £88
DPP-4 inhibitors		
Vildagliptin (Galvus®) 50 mg tablets	50 mg twice daily	£413
Sitagliptin (Januvia®▼) 25 mg, 50 mg and 100mg tablets	100 mg once daily	£432
Linagliptin (Trajenta®▼) 5 mg tablets	5 mg once daily	£432
Other classes of agents		
Repaglinide (non-proprietary) 0.5 mg, 1 mg and 2 mg tablets	0.5 mg–4 mg before each meal*	£44–£87
Acarbose (Glucobay®) 50 mg and 100 mg tablets	50 mg–100 mg three times daily	£89–£164
Pioglitazone (non-proprietary) 15 mg, 30 mg and 45 mg tablets	15 mg–45 mg once daily	£142–£231
**assumes 3 main meals a day* *Costs are based on BNF[28] and MIMS[29] list prices as of 25/07/2012.* *This table does not imply therapeutic equivalence of medicines or the stated doses.*		

6.0 ADDITIONAL INFORMATION

6.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, vildagliptin (Galvus®) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Date of evidence search: 24 July 2012
Date range of evidence search: No date limits were applied to database searches.

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