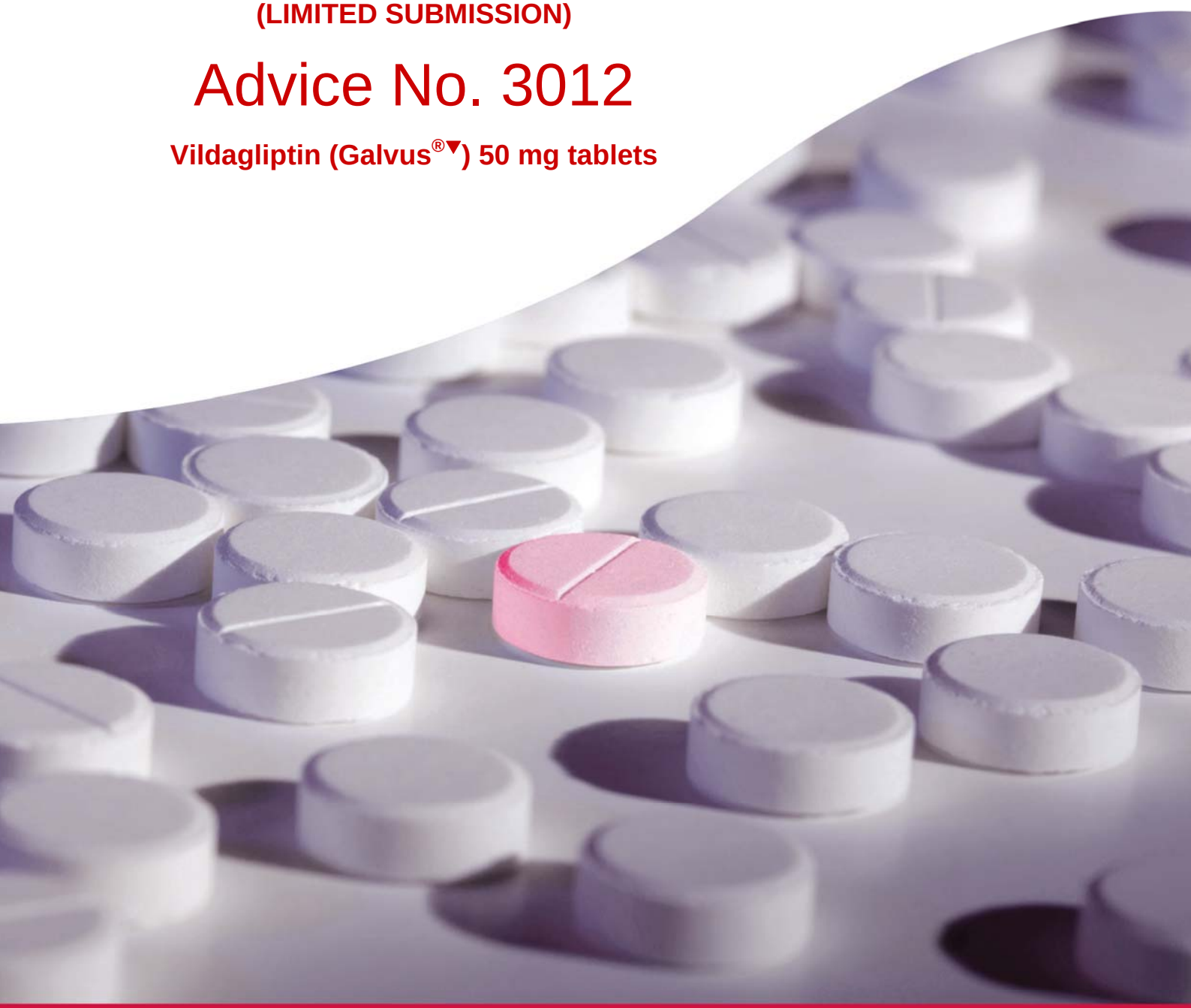
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(LIMITED SUBMISSION)

Advice No. 3012

Vildagliptin (Galvus®▼) 50 mg tablets



In collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University

AWMSG Secretariat Assessment Report – Advice No. 3012
Vildagliptin (Galvus®▼) 50 mg tablets

This assessment report is based on evidence from a limited submission by Novartis Pharmaceuticals Ltd on 23 March 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	This assessment report concerns only a licence extension for the use of vildagliptin 50 mg for the treatment of type 2 diabetes in patients with moderate or severe renal impairment [1,2]. Refer to the Summary of Product Characteristics (SPC) for the full licensed indication.
Dosing	The recommended dose of vildagliptin in patients with moderate or severe renal impairment is 50 mg once daily. Vildagliptin can be administered with or without food[2].
Marketing authorisation date	24 November 2011 for the indication under consideration (first licensed for the treatment of type 2 diabetes mellitus on 26 September 2007)[1,2].

2.0 DECISION CONTEXT

2.1 Background

In 2011, diabetes mellitus affected 160,533 patients in Wales[3] and approximately 85% of these patients have type 2 diabetes mellitus (T2DM)[4]. T2DM is caused by insufficient insulin production by pancreas beta-cells, or the inability of the body to properly utilise endogenous insulin[4]. T2DM is associated with increased cardiovascular risk and microvascular complications such as eye, nerve, and renal damage[5]. Impaired renal function in T2DM patients may preclude the use of first line medicines such as metformin, in which case, alternative oral anti-diabetic agents should be considered[6].

Vildagliptin is an inhibitor of dipeptidyl peptidase (DPP4), an enzyme that catalyses the inactivation of incretins, which in turn, results in an increase in insulin secretion levels. Other DPP4 inhibitors have been licensed for use in T2DM patients with renal impairment, including saxagliptin 2.5 mg (Onglyza®▼) in February 2011 and sitagliptin 25 mg and 50 mg (Januvia®▼) in December 2011, although the severity of renal impairment within which each product is licensed for use, varies[7,8]. The company have estimated that approximately 230 T2DM patients with renal impairment would be eligible to receive treatment with vildagliptin[2].

2.2 Comparators

The comparator requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) was saxagliptin (Onglyza®▼)[7].

2.3 Guidance and related advice

- National Institute for Health and Clinical Excellence (NICE). Type 2 diabetes: the management of type 2 diabetes. Clinical guideline 87 (2009)[5].
- Scottish Intercollegiate Guidelines Network. Management of diabetes. Guideline 116 (2010)[9].

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

- 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[10].
- Linagliptin (Trajenta®▼) is not recommended for use within NHS Wales for the treatment of type 2 diabetes mellitus to improve glycaemic control[11].

AWMSG is concurrently considering a licence extension for the use of sitagliptin (Januvia®▼) 25 mg and 50 mg tablets in patients with moderate or severe renal impairment or with end-stage renal disease (ESRD) requiring haemodialysis or peritoneal dialysis.

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

In light of the lack of direct evidence allowing a comparison of the clinical effectiveness of vildagliptin with any other comparator, the company have provided placebo-controlled clinical data for vildagliptin and saxagliptin in support of their submission[1].

3.1 Clinical effectiveness evidence

3.1.1 The efficacy of vildagliptin versus placebo in T2DM patients with renal impairment[12]

This randomised, double-blind, parallel group placebo controlled trial assessed the efficacy of vildagliptin 50 mg versus placebo in T2DM patients with renal impairment (RI). Recruited patients were aged 18–85 years, with T2DM (glycosylated haemoglobin [HbA1c] between 6.5 and 10%) and moderate or severe RI. Patients (n = 515) were grouped dependent on severity of renal impairment (moderate or severe; severe arm included four patients with ESRD) and randomised to receive either 50 mg vildagliptin once daily (moderate RI: n = 165, severe RI: n = 124) or placebo (moderate RI: n = 129, severe RI: n= 97). Both treatments were taken alongside patients' existing diabetes medication, which included insulin (68.5% and 80.7% in the vildagliptin group [moderate and severe RI, respectively] versus 68.2% and 80.4% in the placebo group [moderate and severe RI, respectively]). The primary endpoint was the between-treatment difference in the adjusted mean change (AMΔ) in HbA1c from baseline at 24 weeks. After 24 weeks of treatment, the between-treatment difference in AMΔ (i.e. AMΔ for vildagliptin minus AMΔ for placebo) was −0.5 ± 0.1% ($p < 0.0001$) in moderate RI (baseline HbA1c = 7.8%) and −0.6% ± 0.1% ($p < 0.0001$) in severe RI (baseline HbA1c = 7.7%). Of those patients with moderate RI, 30.2% achieved target HbA1c (≤ 7%) with vildagliptin versus 24.8% with placebo; this was not statistically significant. However, of those patients with severe RI, a significantly higher percentage of patients achieved target HbA1c in the vildagliptin treatment arm than in placebo arm (48.3% versus 25.0%, respectively; $p = 0.003$)[12].

3.1.2 The efficacy of saxagliptin versus placebo in T2DM patients with renal impairment[13]

This randomised, multicentre, parallel-group, double-blind, placebo-controlled phase III study evaluated the efficacy of saxagliptin 2.5 mg in T2DM patients aged at least 18 years, with inadequate glycaemic control (HbA1c levels: 7–11%) and moderate or severe renal impairment. Patients (n = 170) were randomised 1:1 to receive saxagliptin or placebo. Both treatments were taken alongside patients' existing diabetes medication, which included insulin (83.5% in the saxagliptin group versus 67.1% in the placebo group). The primary efficacy endpoint was the absolute change

in HbA1c from baseline at week 12; this was statistically significantly greater for saxagliptin compared to placebo (p = 0.007). The treatment-related difference in AMΔ in HbA1c was −0.42%. In each RI group, there was a non-significant but numerically larger mean reduction in HbA1c in response to saxagliptin compared to placebo (moderate RI: −0.64% versus −0.05% and severe RI: −0.95 versus −0.5%)[13]. At 52 weeks, the mean change in HbA1c was also significantly lower with saxagliptin than placebo (-1.08% versus −0.36%; p < 0.001)[14].

3.1.3 Evidence of comparative safety

As with comparative efficacy, comparative safety evidence was limited to placebo-based comparisons. The safety and tolerability of both vildagliptin and saxagliptin were generally similar to placebo. In the vildagliptin study, there was a trend for a lower incidence of adverse events (AEs) in vildagliptin treated patients compared to placebo (moderate RI: 67.5% versus 72.9% and severe RI: 72.6% versus 74.2%)[12]. However, in the saxagliptin study, the incidence of AEs was greater in the saxagliptin group compared to placebo (moderate RI: 41.7% vs. 33.3%, severe RI: 61.1% vs. 52.2%)[13].

3.2 AWTTC critique

- In light of the lack of any evidence directly comparing saxagliptin and vildagliptin in patients with T2DM and renal impairment, the company submission was limited to placebo-controlled data only. The company have stated that no formal comparison could be made between the vildagliptin and saxagliptin placebo-controlled trials owing to the following differences in study design and patient demographics:
    - Study duration (24 weeks for vildagliptin versus 12 weeks for saxagliptin)
    - Statistical powering (vildagliptin study powered to detect statistical differences in moderate and severe RI; saxagliptin study powered to detect statistical differences in the overall group)
    - The classification of RI (vildagliptin study used estimated glomerular filtration rate, whereas the saxagliptin study used creatinine clearance as a measurement)
    - Mean baseline HbA1c (in the vildagliptin study, mean baseline HbA1c was 7.7–7.8% versus 8.1–8.5% in the saxagliptin study)
    - Concomitant medication with anti-diabetes treatment (in the vildagliptin study a higher proportion of patients [57.6–70.2%] were receiving additional treatments than in the saxagliptin study [3.5–12.9%]).

  Conclusions on comparative effectiveness are therefore limited to a crude comparison of reductions in HbA1c from baseline: −0.5% (moderate RI) and −0.6% (severe RI) for vildagliptin and −0.42% for saxagliptin (moderate and severe RI)[12,13]. Such comparisons should be interpreted with caution, taking account of the differences between the studies, as highlighted above.
- Although ESRD is not part of the indication under consideration, the vildagliptin study had a low number of patients with ESRD (n = 4). Data for these patients were not reported separately and were included in the severe RI group[12].
- In the saxagliptin study, caution is advised when interpreting the primary endpoint in terms of renal impairment as the baseline distribution of patients was biased towards moderate renal impairment; and the distribution of patients in each renal impairment category after the 12-week and 52-week treatment periods was not disclosed. The Committee for Medicinal Products for Human Use (CHMP) highlighted that the number of patients in the severe renal impairment group was low; the SPC for saxagliptin reflects that experience in this group is limited[15].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

Applicant companies are not required to submit evidence on cost-effectiveness for a limited submission, and literature searches by AWTTC identified no relevant studies.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Using Welsh diabetes prevalence data[3] and market research data, the company estimates that 230 patients with renal impairment are currently eligible to receive DPP4 inhibitors as a part of dual therapy[1]. Cost savings associated with uptake scenarios in the range of 10% to 50% are provided. Additional costs of liver function tests with vildagliptin and renal function tests with sitagliptin are incorporated.

5.1.2 Results of company budget impact analysis

The company concludes that the use of vildagliptin in the treatment of patients with T2DM and moderate or severe renal impairment will result in cost savings driven by a lower acquisition cost of vildagliptin compared to both saxagliptin and sitagliptin.

Table 1. Company-reported cost savings associated with a switch to vildagliptin in the treatment of T2DM patients with moderate or severe renal impairment

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients receiving saxagliptin	39	40	42	43	45
Number of patients receiving sitagliptin	183	190	197	204	211
Total cost (saxagliptin + sitagliptin)	£97,861	£101,624	£105,408	£109,216	£113,046
Savings with 10% switch from saxagliptin	£482	£501	£520	£538	£557
Savings with 50% switch from saxagliptin	£2,412	£2,505	£2,598	£2,692	£2,787
Savings with 10% switch from saxagliptin and sitagliptin	£3,437	£3,570	£3,702	£3,836	£3,971
Savings with 50% switch from saxagliptin and sitagliptin	£17,187	£18,025	£18,512	£19,181	£19,854

5.1.3 AWTTC critique of the budget impact analysis

It is implicitly assumed that vildagliptin is therapeutically equivalent to saxagliptin and sitagliptin, although there are no direct comparative data for vildagliptin and other DPP4 inhibitors specifically in patients with moderate or severe RI or ESRD. The estimates of the number of eligible patients in Wales are based on market research data relating only to DPP4 inhibitors used in (non-metformin) dual oral therapy, although sitagliptin and vildagliptin are also licensed for monotherapy. There is some uncertainty in the potential number of additional patients that will be treated with vildagliptin in its extended licensed indication. However, the acquisition cost of

vildagliptin at the dose recommended for use in patients with moderate or severe RI is around half that of other DPP4 inhibitors (see Table 2).

5.2 Comparative unit costs

Table 2 provides example comparative acquisition costs for DPP4 inhibitors licensed for the treatment of T2DM in adult patients with moderate or severe RI or ESRD. Actual licensed indications differ between the available DPP4 inhibitors, and so relevant SPCs should be consulted for full details.

Table 2. Examples of drug acquisition costs for DPP4 inhibitors in T2DM patients with moderate, severe or end stage renal impairment

Drug	Example doses in renal impairment	Annual cost of treatment
Vildagliptin (Galvus®▼) 50 mg tablets	50 mg once daily	£207
Sitagliptin (Januvia®▼) 25 mg, 50 mg tablets	25–50mg once daily	£434
Saxagliptin (Onglyza®▼) 2.5 mg tablets	2.5 mg once daily	£412
Linagliptin (Trajenta®▼) 5 mg tablets	5 mg once daily	£434
Costs are based on MIMS[16] list prices as of 1 May 2012. *This table does not imply therapeutic equivalence of drugs or the stated doses. See relevant SPCs for licensed indications and full dosing details[2,7,8,17].*		

6.0 ADDITIONAL INFORMATION

6.1 Appropriate place for prescribing

AWTTC is of the opinion that vildagliptin may be appropriate for prescribing by all prescribers within NHS Wales for the indication under consideration.

6.2 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).

6.3 Evidence search

Date of evidence search: 12 April 2012
Date range of evidence search: No date limits were applied to database searches.

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