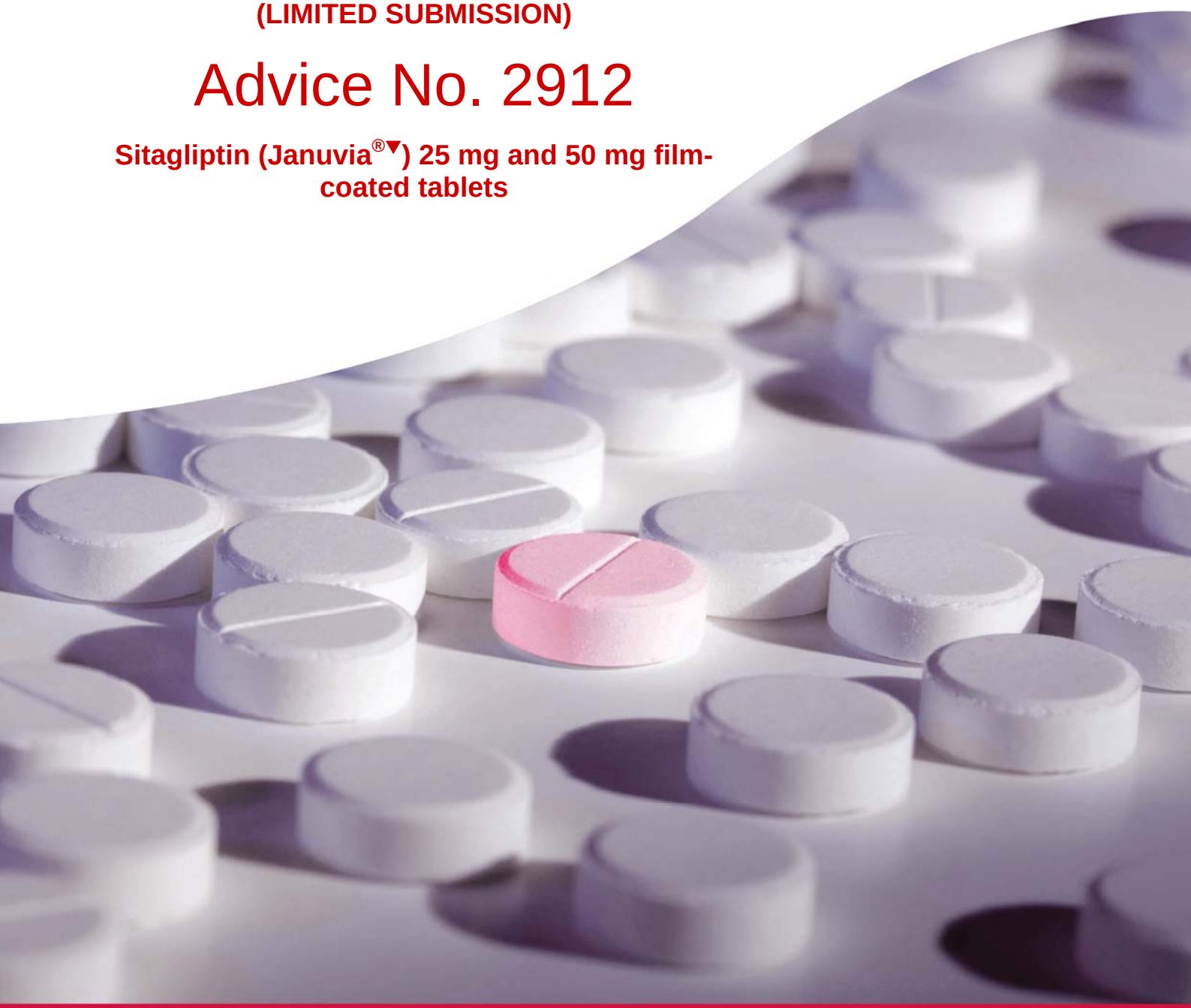
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(LIMITED SUBMISSION)

Advice No. 2912

Sitagliptin (Januvia®▼) 25 mg and 50 mg film-coated tablets



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

AWMSG Secretariat Assessment Report – Advice No. 2912
Sitagliptin (Januvia®▼) 25 mg and 50 mg film-coated tablets

This assessment report is based on evidence from a limited submission by Merck Sharp & Dohme 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 sitagliptin (Januvia®▼) 25 mg and 50 mg for the improvement of glycaemic control in type 2 diabetes mellitus patients with moderate renal impairment (creatinine clearance [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[1]. Refer to the Summary of Product Characteristics (SPC) for the full licensed indication.
Dosing	The recommended dose of sitagliptin is dependent upon renal function. For patients with moderate renal impairment, the dose of sitagliptin is 50 mg once daily. For patients with severe renal impairment or ESRD, the dose of sitagliptin is 25 mg once daily. Sitagliptin can be administered with or without food[2].
Marketing authorisation date	22 December 2011 for the indication under consideration (first licensed for original indication on 21 March 2007)[1,3].

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]. 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[7].

Sitagliptin 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 vildagliptin 50 mg (Galvus®▼) in November 2011, although the severity of renal impairment within which each product is licensed for use varies[8,9]. The company estimate that, in Wales, approximately 458 T2DM patients with renal impairment (RI) would be eligible for treatment with sitagliptin[1] (refer to Section 5 for further details).

2.2 Comparators

The comparators requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) were saxagliptin (Onglyza®▼) and vildagliptin (Galvus®▼). The company suggests that saxagliptin is the most relevant comparator, as at the time of submission, this is the only DPP4 inhibitor recommended by the All Wales Medicines Strategy Group (AWMSG) for use in patients with renal impairment in NHS Wales.

Furthermore, the company cite prescribing data for Wales that suggests usage of vildagliptin to be very low relative to saxagliptin at the time of their submission (see Section 5 for further details)[1]. The company have therefore provided evidence of the comparative effectiveness of sitagliptin compared to saxagliptin only.

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)[6].
- Scottish Intercollegiate Guidelines Network. Management of diabetes. Guideline 116 (2010)[10].

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[11].
- Linagliptin (Trajenta®▼) is not recommended for use within NHS Wales for the treatment of type 2 diabetes mellitus to improve glycaemic control[12].

AWMSG is concurrently considering a licence extension for the use of vildagliptin (Galvus®▼) 50 mg in patients with moderate or severe renal impairment.

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes two studies comparing the use of sitagliptin with glipizide in T2DM patients with either moderate to severe RI[13] or end-stage renal disease (ESRD)[14]. A study comparing the use of sitagliptin in combination with metformin and saxagliptin in combination with metformin was also submitted; however this was carried out in patients with T2DM, but renal impairment was not an inclusion criterion in this study[15]. Although this is the only evidence submitted that directly compares sitagliptin and saxagliptin, it is outside of the indication under consideration and therefore can only be considered as supportive evidence.

3.1 Clinical effectiveness evidence

3.1.1 Sitagliptin versus glipizide in T2DM patients with moderate to severe RI[13]

This phase III, randomised double-blind trial assessed the efficacy and safety of sitagliptin compared with glipizide in patients with T2DM and moderate or severe RI. Eligible patients were ≥ 30 years, not on dialysis at the time of screening and had a glycosylated haemoglobin (HbA1c) level ≥ 7% and ≤ 9%. After a 2 week single-blind placebo run in period, patients (n = 426) were randomised 1:1 to receive either sitagliptin (n = 213) or glipizide (n = 213). Sitagliptin was administered at a dose of 50 mg once daily for moderate RI or 25 mg once daily for severe RI (with a dose adjustment for patients whose renal status transitioned from moderate to severe); glipizide was initiated at a dose of 2.5 mg once daily for severe RI (titrated up or down, based on glycaemic control, as considered appropriate by the investigator to a maximum dose of 10 mg twice daily). The primary endpoint of the least-squares (LS) mean change from baseline (7.7–7.8%) in HbA1c at week 54 was −0.75% for sitagliptin and −0.64% for glipizide. The between-group difference was −0.11% in the per protocol population, which met the pre-defined criteria for non-inferiority between the two treatments[13].

3.1.2 Sitagliptin versus glipizide in T2DM patients with ESRD[14]

This phase III randomised double-blind trial assessed the efficacy and safety of sitagliptin compared with glipizide in patients with T2DM and ESRD. Patient eligibility has been detailed in Section 3.1.1; however, patients in this population were receiving dialysis. Patients (n = 129) were randomised 1:1 to receive doses of either sitagliptin 25 mg once daily or glipizide initiated at a dose of 2.5 mg once daily (titrated up or down as considered appropriate by the investigator to a maximum dose of 10 mg twice daily). The primary endpoint of the LS mean change in HbA1c from baseline (7.8–7.9%) at week 54 was −0.72% and −0.87% for sitagliptin and glipizide, respectively[14].

3.1.3 Supportive study: sitagliptin in combination with metformin versus saxagliptin in combination with metformin in patients with T2DM[15]

This multicentre randomised phase III trial assessed efficacy and safety of sitagliptin in combination with metformin, compared to saxagliptin in combination with metformin in adult patients with T2DM. Eligible patients (n = 801) were randomised 1:1 to receive either sitagliptin 100 mg once daily (n = 398) or saxagliptin 5 mg once daily (n = 403), in combination with metformin. The primary endpoint was the adjusted mean change in HbA1c) at 18 weeks: this was −0.62% and −0.52% for sitagliptin and saxagliptin, respectively. The between-group difference was 0.09% (95% CI, −0.01% to −0.20%), which demonstrated non-inferiority between the two treatments, as defined by the pre-specified statistical criteria. Secondary endpoints were supportive of these findings[15].

3.1.4 Evidence of comparative safety

Sitagliptin was generally found to be well tolerated in the studies described above[13–15]. In the study comparing sitagliptin with glipizide in T2DM patients with moderate to severe RI, treatment related adverse events (AEs) occurred in 12.9% of sitagliptin-treated patients versus 18.4% of glipizide-treated patients[16]. The sitagliptin group had a significantly lower incidence of symptomatic hypoglycaemia AEs (6.2% for sitagliptin versus 17% for glipizide; $p < 0.001$) and nausea (0% versus 2.4%; $p = 0.025$) compared to glipizide[13]. Treatment related AEs were found in 15.6% versus 20.0% of T2DM patients with ESRD receiving sitagliptin and glipizide, respectively[17]. Higher incidences of cellulitis and headache were also more frequent in sitagliptin-treated patients within this population group (6.3% versus 0%, respectively for both)[14].

3.2 AWTTC critique

- The company submission included data on two phase III trials comparing sitagliptin with glipizide in moderate to severe RI and ESRD. Both trials demonstrated comparable efficacy of sitagliptin, as demonstrated by mean change in HbA1c from baseline[13,14]. However it should be noted that glipizide was not a comparator requested by AWTTC.
- The company submission highlighted that no trials had been conducted where sitagliptin had been directly compared to saxagliptin in patients with RI or ESRD; therefore a study comparing the use of sitagliptin with saxagliptin in combination with metformin in T2DM patients was included[1,15]. Due to the indication differences, i.e. patients without RI or ESRD, the dosage of sitagliptin administered in the included trial (100 mg)[15] is different to the dosage under appraisal (25 mg/50 mg)[1]. In addition, the dose of saxagliptin is also different in the included study (5 mg)[15] compared to the dose recommended for use in moderate or severe RI (2.5 mg)[9]. It should also be noted that metformin is contraindicated in patients with moderate or severe renal impairment[18].
- In comparison to saxagliptin, sitagliptin is licensed for use in monotherapy as well as triple therapy and may therefore be used in a broader range of patients with T2DM and RI. Unlike saxagliptin, sitagliptin may be used in patients with ESRD across all licensed indications[1,2].

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 the AWTTC identified no relevant studies.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company estimates there are currently 10,280 patients in Wales with type 2 diabetes mellitus (T2DM) and a creatinine clearance of < 50 ml/min[1]. Using patient-level data provided by a market research company, it is estimated that 458 people with T2DM and a creatinine clearance of < 50 ml/min would be eligible for treatment with sitagliptin in Wales. The company estimates that sitagliptin already accounts for 82% of all DPP4 inhibitors prescribed in Wales, and that saxagliptin is the main comparator: it is the only DPP4 inhibitor that has been recommended by AWMSG for use in patients with renal impairment in NHS Wales, and prescribing of vildagliptin is currently very low[1]. Therefore, based on an annual increase in prevalence of 0.9%, and assuming sitagliptin takes 100% market share, it is anticipated that there would be an additional 83 patients in year 1 that could be prescribed sitagliptin within the extended license indication, increasing to 86 in year 5.

5.1.2 Results of company budget impact analysis

Based on a difference in annual treatment costs of £21.64 per patient (see Table 1), displacement of saxagliptin by sitagliptin is estimated to cost an additional £1,788 in year 1, rising to £1,856 in year five (giving a total additional cost of £9,110 over the five years). The company also highlights differences in the licensed indications that may represent advantages for sitagliptin over saxagliptin, including its use in patients with end stage renal disease, and its use as monotherapy or in triple therapy (see Section 3.2)[1].

5.1.3 AWTTC critique of the budget impact analysis

It is implicitly assumed that sitagliptin and saxagliptin are therapeutically equivalent, although there are no direct comparative data for sitagliptin and other DPP4 inhibitors specifically in patients with moderate, severe or end stage renal impairment. The estimates of the number of eligible patients in Wales are based on market research data, to which the company has made assumptions on the proportion with creatinine clearance of < 50 ml/min[1]. Combined with the fact that vildagliptin is also now licensed for use in patients with ESRD, there is some uncertainty in the potential number of additional patients who will be treated with sitagliptin in its extended licensed indication. However, the actual per patient difference in annual acquisition costs is small.

5.2 Comparative unit costs

Table 1 provides example comparative acquisition costs for DPP4 inhibitors licensed for the treatment of T2DM in adult patients with moderate, severe or end stage renal impairment. Actual licensed indications differ between the available DPP4 inhibitors, and so relevant SPCs should be consulted for full details.

Table 1. Examples of drug acquisition costs for DPP4 inhibitors in adult patients with moderate, severe or end stage renal impairment

Drug	Example doses in renal impairment	Annual cost of treatment
Sitagliptin (Januvia®▼) 25 mg, 50 mg tablets	25–50 mg once daily	£434
Saxagliptin (Onglyza®▼) 2.5 mg tablets	2.5 mg once daily	£412
Vildagliptin (Galvus®▼) 50 mg tablets	50 mg once daily	£207
Linagliptin (Trajenta®▼) 5 mg tablets	5 mg once daily	£434
Costs are based on MIMS[19] 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[2,8,9,20].*		

6.0 ADDITIONAL INFORMATION

6.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, sitagliptin 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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