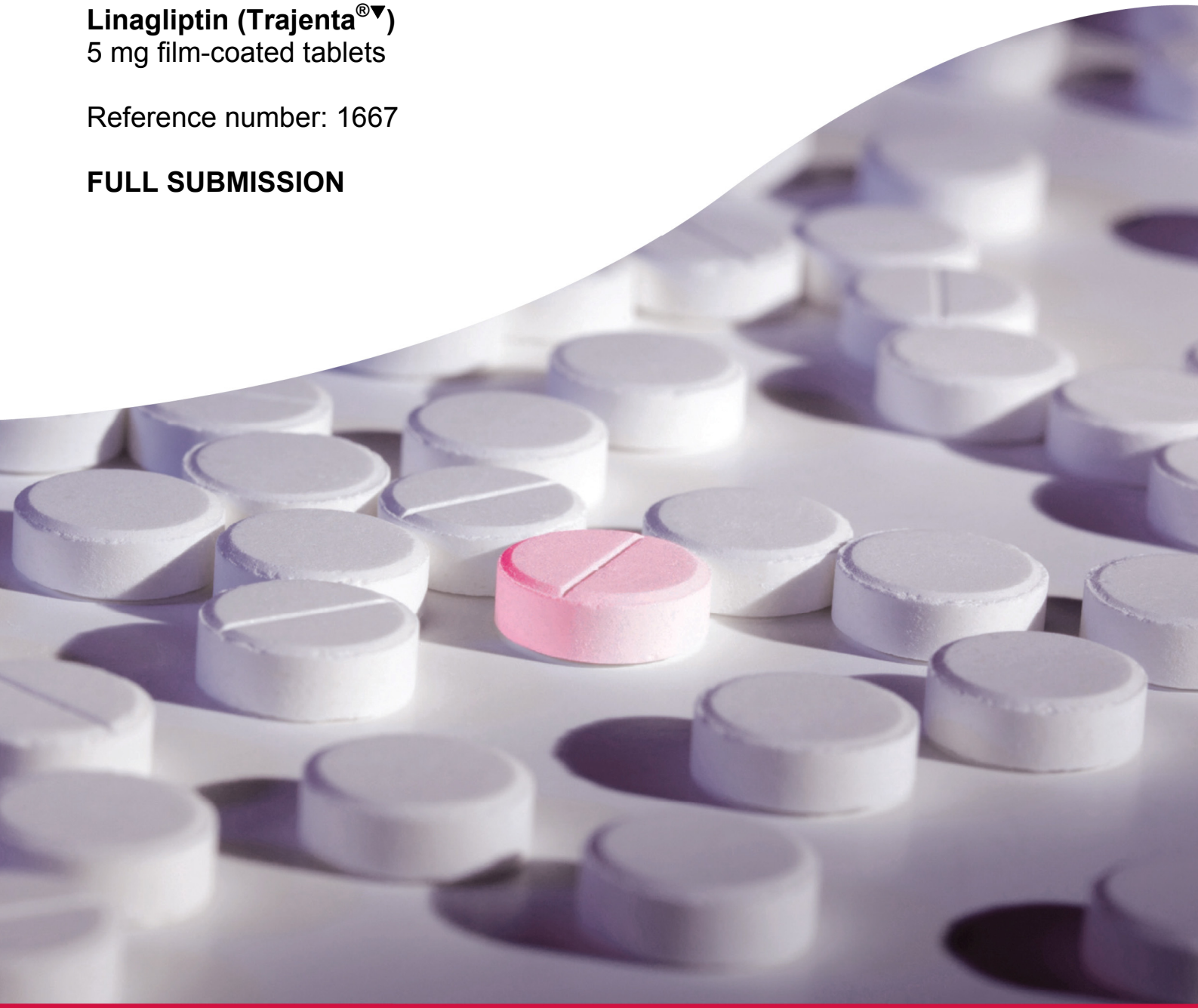
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Linagliptin (Trajenta®▼)
5 mg film-coated tablets

Reference number: 1667

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Linagliptin (Trajenta®▼) 5 mg film-coated tablets

This assessment report is based on evidence submitted by Boehringer Ingelheim/Eli Lilly & Co Ltd on 2 October 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Linagliptin (Trajenta®▼) is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults: as monotherapy • in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to intolerance, or contraindicated due to renal impairment; as combination therapy • in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control; • in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control; and • in combination with insulin with or without metformin, when this regimen alone, with diet and exercise, does not provide adequate glycaemic control[2].
Dosing	The dose of linagliptin is 5 mg once daily. When linagliptin is added to metformin, the dose of metformin should be maintained, and linagliptin administered concomitantly. When linagliptin is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia. Refer to the Summary of Product Characteristics (SPC) for more information[2].
Marketing authorisation date	Linagliptin was originally licensed on 25 August 2011. On 24 October 2012, linagliptin received a licence extension to include use in combination with insulin with or without metformin, when this regimen alone, with diet and exercise, does not provide adequate glycaemic control[3]. Refer to Section 2.1 for further details.

2.0 DECISION CONTEXT

2.1 Background

In 2011, diabetes mellitus affected 160,533 patients in Wales[4]; 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[6]. NICE CG87 suggests adding a dipeptidyl peptidase (DPP-4) inhibitor to a first-line therapy (metformin or sulphonylurea) when control of blood glucose remains or becomes inadequate[6].

Linagliptin is a DPP-4 inhibitor which increases the levels of active incretin hormones, resulting in an increase in insulin secretion levels and a reduction in glycaemia[2]. The company estimates that, according to the licensed indication, approximately 58,000 patients would theoretically be eligible for linagliptin treatment in Wales; however, they state that the proportion of eligible patients that are likely to receive linagliptin would be lower[1].

On 24 October 2012, linagliptin received a licence extension to include use in combination with insulin with or without metformin, when this regimen alone, with diet and exercise, does not provide adequate glycaemic control[3]. The remaining indications detailed in Section 1.0 were licensed prior to this, on 25 August 2011. The entire licensed indication, as stated in Section 1.0, is under consideration by the All Wales Medicine Strategy Group (AWMSG).

2.2 Comparators

The comparators requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) were:

- Sitagliptin (Januvia®)
- Vildagliptin (Galvus®▼)
- Saxagliptin (Onglyza®)

In their submission, the applicant company have only provided comparative data for sitagliptin. They state that sitagliptin is the most widely used DPP-4 inhibitor in Wales (82%), and that it is the only comparator with a licensed indication that closely matches that of linagliptin[1].

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].
- National Horizon Scanning Centre. Linagliptin (Ondero) for type 2 diabetes mellitus – monotherapy or add-on therapy (2010)[8].

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)[9].
- 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 requiring haemodialysis or peritoneal dialysis (2012)[10].
- 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)[11].
- Linagliptin (Trajenta®▼) is not recommended for use within NHS Wales for the treatment of type 2 diabetes mellitus to improve glycaemic control (2012)[12].
- 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)[13].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The applicant company have provided a model-based meta-analysis, which provided information on the efficacy of linagliptin versus sitagliptin. In addition, the submission included details of four pivotal phase III clinical trials, which evaluated the efficacy and safety of linagliptin 5 mg once daily in monotherapy, dual therapy and triple therapy[14–17]. Other phase II and phase III trials were included in the company submission but will not be discussed further; an overview of the relevant phase III studies can be found in Appendix 1.

3.1 Model-based meta-analysis

In the absence of any direct data comparing linagliptin with sitagliptin, the company performed a model-based meta-analysis to evaluate the comparative efficacy of the two treatments, using HbA1c as a primary endpoint. The company performed a literature review to identify all relevant clinical trials of linagliptin and sitagliptin; trials were only included if they met the following criteria:

- conducted in T2DM patients
- involved treatment with linagliptin or sitagliptin over a period of at least 12 weeks
- assessed HbA1c outcomes.

A total of 17 eligible studies of linagliptin and 35 eligible studies of sitagliptin were identified. For both treatments, the studies included encompassed use of the medicines both as monotherapy and in combination with other oral antidiabetic agents (OAD) such as metformin, pioglitazone and/or a sulphonylurea[1].

Results from the model-based meta-analysis show that, at 24 weeks, patients treated with linagliptin 5 mg once daily experienced a reduction in HbA1c by 0.720 percentage points (90% credible interval [CrI] 0.648–0.799). A similar result was observed with sitagliptin 100 mg once daily (0.786 percentage points; 90% CrI 0.700–0.873). The company conclude that the difference between the two treatments was not clinically meaningful (all base case model simulations yielded a difference in HbA1c reduction < 0.3%)[1].

3.2 Phase III studies

3.2.1 Linagliptin monotherapy

Study 1218.16 was a randomised, double-blind, parallel group, multicentre, placebo-controlled phase III trial designed to assess the efficacy of a once daily dose of linagliptin 5 mg over 24 weeks. The study included adult T2DM patients with a body mass index (BMI) ≤ 40 kg/m^2 and inadequate glycaemic control (HbA1c 7.0%–10.0%) who were either treatment-naive or had previously received one OAD. Patients were randomised 2:1 to receive either linagliptin 5 mg (n = 336) or placebo (n = 167). The primary endpoint was change from baseline in HbA1c, adjusted for baseline HbA1c and previous OAD. This was met in favour of linagliptin over placebo: the adjusted mean change in HbA1c from baseline to 24 weeks was −0.44 ± 0.05% and +0.25 ± 0.07%, for the linagliptin and placebo arms respectively. The adjusted mean difference in HbA1c between linagliptin and placebo was −0.69% ($p < 0.0001$). This was supported by secondary analyses[14].

3.2.2 Linagliptin compared to placebo with metformin background therapy

Study 1218.17 was a randomised, double-blind, parallel group, multicentre, placebo-controlled phase III trial, which investigated the efficacy and safety of linagliptin 5 mg (plus metformin) over 24 weeks. The study included adult T2DM patients with a BMI ≤ 40 kg/m^2 and inadequate glycaemic control (HbA1c 7.0%–10.0%) despite metformin treatment (≥ 1,500 mg/day). Patients were randomised 3:1 to receive either linagliptin (n = 524) or placebo (n = 177), and were requested to maintain their metformin

background therapy throughout the study without modifying the dose or dosing regimen.

The primary endpoint of this study was the change from baseline in HbA1c after 24 weeks of treatment; this was met in favour of linagliptin over placebo. The adjusted mean change in HbA1c was −0.49 ± 0.04% and +0.15 ± 0.06%, for the linagliptin and placebo arms respectively. This equated to a treatment difference of −0.64% (95% CI −0.78 to −0.50; p < 0.0001). Sensitivity analyses and secondary endpoints supported this finding[15].

3.2.3 Linagliptin plus metformin plus sulphonylurea

Study 1218.18 was a randomised, double-blind, parallel group, multicentre, placebo-controlled phase III trial, which investigated the efficacy, safety and tolerability of linagliptin 5 mg once daily compared with placebo in adult T2DM patients over a 24 week period. Patients included in the study had a BMI ≤ 40 kg/m^2 and HbA1c levels between 7.0% and 10.0%, despite receiving a total daily dose of metformin ≥ 1,500 mg/day and the maximum tolerated dose of sulphonylurea. Patients were randomised to receive either linagliptin 5 mg (n = 793) or placebo (n = 265). The primary endpoint was the mean change in HbA1c levels from baseline to 24 weeks. This was found to be superior in the linagliptin group compared to placebo with an adjusted mean change in HbA1c of −0.62% (95% CI −0.73 to −0.50; p < 0.0001). Secondary endpoint analyses supported this finding[16].

3.2.4 Linagliptin plus insulin

Study 1218.36 was a randomised, double-blind, parallel group, multicentre, placebo-controlled phase III trial designed to assess the efficacy and safety of linagliptin 5 mg once daily versus placebo, administered for at least 52 weeks as add-on to basal insulin therapy. The study included adult patients with T2DM, a BMI ≤ 45 kg/m^2, and with insufficient glycaemic control (HbA1c 7.0%–10.0%). Patients were randomised 1:1 to receive either linagliptin 5 mg (n = 633) or placebo (n = 630). The background dose of basal insulin was to remain stable during the first 24 weeks of treatment; the dose of other OAD was to remain stable throughout the whole study. The primary endpoint was the change from baseline in HbA1c after 24 weeks of treatment. Linagliptin 5 mg was found to be superior to placebo: the adjusted mean change in HbA1c was −0.58% ± 0.08 in the linagliptin 5 mg group compared to 0.07% ± 0.08 in the placebo group, with a treatment difference of −0.65% (95% CI −0.74, −0.55; p < 0.0001). This finding was supported by secondary endpoint analyses[17].

3.3 Comparative safety

In all placebo controlled trials, the overall incidence of adverse events (AEs) in patients treated with linagliptin 5 mg (n = 5,955) was similar to that of placebo (60.3% versus 63.1%). Discontinuation due to AEs was lower in patients receiving linagliptin compared to placebo (4.4% vs. 3.3%). The most frequently reported AE was hypoglycaemia (6.2%)[1,2]. The Summary of Product Characteristics (SPC) states that sulphonylurea and insulin are known causes of hypoglycaemia; therefore, caution is advised when linagliptin is used in combination therapy with a sulphonylurea and/or insulin. A dose reduction of the sulphonylurea or insulin may be required[2].

The open-label extension study 1218.40 primarily evaluated the long-term safety and tolerability of linagliptin over 78 weeks, in patients who had participated in studies 1218.16, 1218.17, 1218.18 and 1218.15 (the latter is not discussed in Section 3.2, as linagliptin is not indicated in combination with pioglitazone). Overall, 1,253 (81.8%) linagliptin-treated patients reported at least one AE during the 78-week extension phase. When stratified according to previous treatment regimen, the highest incidence of AEs was noted in participants receiving metformin plus a sulphonylurea background (84.2%), followed by patients receiving metformin background therapy (81.6%) and linagliptin monotherapy (78.8%). Linagliptin was found to be well tolerated; AEs

associated with treatment were mild to moderate. The most frequently occurring AEs were hyperglycaemia (24.5%), hypoglycaemia (13.6%) and nasopharyngitis (10.7%)[18].

3.4 AWTTC critique

- There are no active control trials for linagliptin versus sitagliptin. In the absence of direct evidence, the applicant company carried out a model-based meta-analysis to assess the comparative efficacy of the two products. The model-based meta-analysis is a relatively new methodology in the setting of health technology assessment, which has both advantages and disadvantages (see Section 4.1 for further details)[1].
- The applicant company have not included comparative data for saxagliptin or vildagliptin on the basis that sitagliptin is the most widely prescribed DPP-4 inhibitor in Wales[1]. However, saxagliptin and vildagliptin are both in routine use in Wales.
- It should be noted that some of the studies included in the company submission are, at the time of writing, not published and therefore not peer-reviewed (see Appendix 1 for details).
- The meta-analyses conducted by the applicant company consider changes in HbA1c only. Other treatment outcomes, such as fasting plasma glucose and serum lipids were not compared for linagliptin and sitagliptin. AE profiles are assumed to be comparable[1].
- The applicant company highlight linagliptin as an alternative to other DPP-4 inhibitors in patients with renal impairment, as linagliptin is only partially excreted (5%) by the renal route, and so no dose adjustment would be required. Therefore, the company state that the use of linagliptin would avoid the need for renal function monitoring[1]. The efficacy of linagliptin in T2DM patients with renal impairment is investigated in study 1218.43[19]. However, it should be noted that metformin is contraindicated in patients with creatinine clearance < 60 ml/min[20]. Therefore, in this instance, linagliptin use may only be appropriate as monotherapy or in combination with insulin without metformin.
- Linagliptin is indicated in monotherapy as well as combination therapy and may therefore be used in a broader range of patients with T2DM and renal impairment than other DPP-4 inhibitors[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 (CMA) of linagliptin 5 mg once daily in its full licensed indications, compared to sitagliptin 100 mg once daily for the treatment of T2DM to improve glycaemic control in adults. AWTTC requested sitagliptin, vildagliptin and saxagliptin as the most appropriate comparators for linagliptin. The company selected sitagliptin only, on the basis that this is the most widely prescribed DPP-4 inhibitor in Wales (82%) and they consider its licensed indications are closest of all other DPP-4 inhibitors to those of linagliptin.

There are no direct comparative trials of linagliptin and sitagliptin. The CMA assumes therapeutic equivalence of linagliptin and sitagliptin based on results of model-based meta-analyses that indirectly compare changes from baseline in HbA1c from a number of randomised trials that cover the range of the licensed indications. The statistical modelling approach is intended to control for differences in the included trials' designs, comparators, drug doses, population characteristics and treatment combinations. Only acquisition costs over one year are considered in the CMA, as other costs associated with treatment initiation, monitoring, AEs and management of the long-term complications of diabetes are assumed to be the same for patients taking linagliptin and sitagliptin.

4.1.2 Results
The estimated annual treatment cost is £434 per patient for both linagliptin and sitagliptin. Linagliptin is therefore assumed to be as cost-effective as sitagliptin in improving glycaemic control in adults with T2DM across all of its licensed indications.

4.1.3 AWTTC critique
The reliability of the CMA presented by the applicant company is dependent upon the extent to which linagliptin has been demonstrated to be therapeutically equivalent to the relevant comparator(s). In the absence of direct comparative data the company has based its assumption of therapeutic equivalence of linagliptin and sitagliptin on model-based indirect comparisons of a wide range of trials, spanning all relevant licensed indications[1]. Sitagliptin consistently produced numerically greater reductions in HbA1c than linagliptin, although the company reports that all differences in HbA1c are < 0.3% and are not clinically relevant. The CMA framework precludes exploration of the impact of uncertainty in estimates of effectiveness.

Strengths of the economic evidence include:

- In the absence of direct comparative data, the applicant company has undertaken a systematic review of relevant clinical trials, and has conducted extensive indirect model-based meta-analyses to facilitate comparison of effectiveness across all licensed indications.

Limitations of the economic evidence include:

- Due to the lack of direct comparative data for linagliptin and sitagliptin, therapeutic equivalence is assumed based on results of indirect comparisons of trial data conducted using model-based meta-analysis. The meta-analyses conducted by the company consider changes in HbA1c only. Other treatment outcomes, such as fasting plasma glucose and serum lipids were not compared for linagliptin and sitagliptin. AE profiles are assumed to be comparable.
- The company acknowledges that model-based meta-analysis is a relatively new methodology in the setting of health technology assessment and, as such, a well-developed suite of accepted diagnostics for model assessment is not available. An independent Bayesian statistics expert was commissioned by the company to validate the model.
- A wide range of studies were included in the model-based meta-analyses and it is unclear if the covariates considered in the model to adjust for differences in trial designs and populations would account for all potential sources of heterogeneity; however, a wide range of obvious potential covariates were explored.
- The CMA approach precludes exploration of uncertainty in effectiveness estimates. Sitagliptin consistently produced numerically greater reductions in HbA1c than linagliptin, although the differences in HbA1c reductions are all < 0.3%, which the company considers is demonstration of no clinically important differences in efficacy between linagliptin and sitagliptin.

4.2 Review of published evidence on cost-effectiveness
Standard literature searches have not identified any published economic evidence on the cost-effectiveness of linagliptin for the treatment of T2DM.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence
5.1.1 Context and methods
Based on the Welsh Government Quality and Outcomes Framework disease register[21], the company estimates that there were 160,533 adult patients with diabetes in

2010/2011 in Wales. T2DM accounts for approximately 90% of these cases. Assuming a 4.4% increase in the prevalence of diabetes each year, the estimated number of patients is expected to increase from 157,000 in 2013 to 187,000 in 2017. According to company-obtained marketing data, approximately 11.4% of T2DM patients currently receive a DPP-4 inhibitor.

5.1.2 Results of company budget impact analysis

The estimated numbers of patients and the associated costs over the five-year period are summarised in Table 1. The total annual cost of treatment with linagliptin in Wales is estimated to be £1,017,425 in year one after introduction, rising to £2,101,462 in year five. The company anticipates that linagliptin will displace sitagliptin, which is currently the most widely prescribed DPP-4 inhibitor in Wales. As linagliptin has the same list price and is assumed to be equivalent in all outcomes to sitagliptin, the impact of linagliptin on the NHS Wales budget is expected to be neutral.

Table 1. Company-reported costs associated with linagliptin treatment of adult patients with type 2 diabetes mellitus (Commercial in confidence data has been removed).

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of DPP-4 inhibitor eligible patients	17,895	18,678	19,495	20,347	21,237
Sitagliptin displaced costs	£1,017,425	£1,256,463	£1,438,315	£1,757,298	£2,101,462
Total net costs	0	0	0	0	0

No alternative scenario analyses have been presented to address the uncertainty of the cost estimates.

5.1.3 AWTTC critique of the company's budget impact estimates

The company has made reasonable efforts to estimate relevant patient numbers. The analysis considers linagliptin as an alternative to sitagliptin only, although other DPP-4 inhibitors could be relevant comparators. As therapeutic equivalence of linagliptin and sitagliptin is assumed, no other resource use or costs are considered in the analysis. Both linagliptin and sitagliptin are available as fixed combination tablets with metformin (Jentadueto®▼ and Janumet®, respectively), which are less costly than the equivalent doses of linagliptin or sitagliptin given separately to metformin, although company-obtained prescribing data suggest that current use of Janumet® in Wales is relatively low.

5.2 Comparative unit costs

The company reports that linagliptin will only be considered for use as an alternative to other DPP-4 inhibitors, and that the majority of its use will be as a component of dual or triple therapy; however, a range of other agents have indications that may be considered to overlap with the linagliptin licensed indications. Table 2 provides comparative acquisition costs of alternative DPP-4 inhibitors. Current NICE Clinical Guidelines[6] on the treatment of T2DM should be consulted, along with the most recent list prices of alternative classes of agents.

Table 2. Comparative acquisition costs of DPP-4 inhibitors

Product	Example regimen	Cost per year (£)
Trajenta®▼ (linagliptin) 5 mg tablets	5 mg once daily	434
Jentadueto®▼ (linagliptin 2.5 mg/ metformin 850 mg); Jentadueto®▼ (linagliptin 2.5 mg/ metformin 1,000 mg); tablets	2.5 mg/850 mg twice daily to 2.5 mg/1,000 mg twice daily	434*
Januvia® (sitagliptin) 25 mg, 50 mg and 100 mg tablets	100 mg once daily	434
Janumet® (sitagliptin 50 mg/ metformin1,000 mg) tablets	50 mg/1,000 mg twice daily	451
Onglyza® (saxagliptin) 2.5 mg and 5 mg tablets	5 mg daily	412
Galvus®▼ (vildagliptin) 50 mg tablets	50 mg twice daily	411
Eucreas®▼ (vildagliptin 50 mg/metformin 850 mg), Eucreas®▼ (vildagliptin 50 mg/metformin 1,000 mg) tablets	50 mg/850 mg twice daily to 50 mg/1,000 mg twice daily	413
See relevant SPCs for full dosing details[2,22–27]. Costs are based on MIMS[28] list prices as of 5 December 2012. This table does not imply therapeutic equivalence of drugs or the stated doses. * Jentadueto®▼ (linagliptin/metformin) tablets may be subject to appraisal by AWMSG, pending the outcome of the appraisal of Trajenta®▼ (linagliptin) tablets.		

6.0 ADDITIONAL INFORMATION

6.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, linagliptin (Trajenta®▼) may be appropriate for prescribing by all prescribers within NHS Wales for the indication under consideration.

6.2 Ongoing studies

The company submission highlighted one ongoing study for which results are likely to be available within 6–12 months[1]:

- Study 1218.64: Linagliptin in patients with moderate to severe renal impairment (12 weeks versus placebo and 40 weeks versus sulphonylurea)[29].

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: 19, 20 and 22 November 2012
Date range of evidence search: No date limits were applied to database searches.

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Appendix 1.

Table 1. Overview of phase III studies of linagliptin in the treatment of T2DM

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Primary endpoints
Monotherapy						
1218.16, Del Prato 2011[14]	Phase III, randomised, double-blind, placebo-controlled, multicentre, 24 week study.	503	Patients 18–80 years of age with a BMI of ≤ 40 kg/m^2, undergoing washout of previous antidiabetic medication: 6.5% ≤ HbA1c ≤ 9.0%; patients not undergoing washout of previous antidiabetic medication: 7.0% ≤ HbA1c ≤ 10.0%.	Male patients: 48.3% Age (years, mean [SD]): 55.7 (10.2)	Linagliptin 5 mg/day for 24 weeks.	Change from baseline HbA1c after 24 weeks. Superiority of linagliptin over placebo. Adjusted mean change: −0.69% ($p < 0.001$)
1218.50* [30]	Phase III, randomised, double-blind, placebo-controlled, multicentre, 18 week study. Followed by a double-blind, active-controlled 34-week extension period.	227	Patients 18–80 years of age with a BMI of ≤ 40 kg/m^2, undergoing washout of previous antidiabetic medication: 6.5% ≤ HbA1c ≤ 9.0%; patients not undergoing washout of previous antidiabetic medication: 7.0% ≤ HbA1c ≤ 10.0%.	Male patients: 34.8% Age (mean years): 56.6	Part 1: linagliptin 5 mg/day for 18 weeks. Part 2: extension phase linagliptin 5 mg/day or glimepiride for 34 weeks.	Change from baseline HbA1c after 18 weeks. Superiority of linagliptin over placebo. Adjusted mean change: −0.60% (95%CI: −0.88, −0.32; $p < 0.001$)
In combination with metformin						
1218.17, Taskinen 2011[15]	Phase III, randomised, double-blind, placebo-controlled, multicentre, 24 week study.	701	Patients 18–80 years of age with a BMI of ≤ 40 kg/m^2. Patients undergoing washout of previous antidiabetic medication: 6.5% ≤ HbA1c ≤ 9.0%; patients not undergoing washout of previous antidiabetic medication: 7.0% ≤ HbA1c ≤ 10.0%.	Male patients: 54%, Age (years, mean [SD]): 56.5 [10.3]	Linagliptin 5 mg/day for 24 weeks with a background therapy of metformin (1500 mg/day).	Change from baseline HbA1c after 24 weeks. Superiority of linagliptin over placebo. Adjusted mean change: −0.64% (95% CI −0.78 to −0.50; $p < 0.0001$)
1218.20, Gallwitz 2011[31]	Phase III, randomised, double-blind, active-controlled, multicentre, 104 week study.	1,552	Patients 18–80 years of age with a BMI of ≤ 40 kg/m^2. Patients with previous metformin monotherapy or metformin plus not more than one other oral antidiabetic agent (unchanged for 10 weeks). For patients undergoing washout of previous antidiabetic medication: 6.0% ≤ HbA1c ≤ 9.0%; patients not undergoing washout of previous antidiabetic medication 6.5% ≤ HbA1c ≤ 10.0%	Male patients: 60%, Age (years, mean [SD]): linagliptin, 59.8 (9.4); placebo, 59.8 (9.4)	Linagliptin 5 mg/day compared to glimepiride 1–4 mg/day over 104 weeks.	Change from baseline HBA1c after 52 weeks and 104 weeks. Non-inferiority of linagliptin compared to glimepiride. Adjusted mean change 0.2% (97.5% CI: 0.094, 0.299)

Table 1. Continued. Overview of phase III studies of linagliptin in the treatment of T2DM

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Primary endpoint
In combination with sulphonylurea						
1218.35* [32]	Phase III, randomised, double-blind, placebo-controlled, multicentre, 18 week study.	245	Patients 18–80 years of age. Patients undergoing washout of previous medication: 7.0% ≤ HbA1c ≤ 9.0%; patients not undergoing washout of previous medication: 7.5% ≤ HbA1c ≤ 10.0%;	Male patients: linagliptin group, 61.9%; placebo group, 47.8%, Age (years, mean): 56.9	Linagliptin 5 mg/day for 24 weeks with a background of sulphonylurea.	Change from baseline HbA1c after 18 weeks. Superiority of linagliptin over placebo. Adjusted mean change: −0.47% (95% CI −0.70, −0.24; p < 0.0001)
In combination with metformin and sulphonylurea						
1218.18, Owens 2011 [16]	Phase III, randomised, double-blind, placebo controlled, multicentre, 24 week study.	1,058	Patients 18–80 years of age with a BMI of ≤ 40 kg/m². 7.0% ≤ HbA1c ≤ 10.0% despite therapy with metformin and sulphonylurea.	Male patients: 47.2%, Age (years, mean [SD]): 58.1 (9.8)	Linagliptin 5 mg/day for 24 weeks with a background of metformin and a sulphonylurea.	Change from baseline HbA1c after 24 weeks. Superiority of linagliptin over placebo. Adjusted mean change: −0.62% (95% CI −0.73 to −0.50; p < 0.0001)
In combination with insulin						
1218.36* [17]	Phase III, randomised, double-blind, placebo controlled, multicentre, 24 week study followed by 52 week extension study.	1,263	Patients ≥18 years who were being treated with subcutaneous basal insulin alone or in combination with metformin and/or pioglitazone and BMI ≤ 45 kg/m². ≥ 7.0% ≤ HbA1c ≤ 10.0%.	Male patients: 52.2%, Age (years, mean): 60.0	Linagliptin 5 mg/day with a stable background of insulin for 24 weeks, after which insulin adjustment was permitted. Background therapy with metformin and/or pioglitazone.	Change from baseline HbA1c after 24 weeks. Superiority of linagliptin over placebo. Adjusted mean change: −0.65% (95% CI −0.74, −0.55; p < 0.0001)

Table 1. Continued. Overview of phase III studies of linagliptin in the treatment of T2DM

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Primary endpoint
Mixed treatment combinations						
1218.43*[19]	Phase III, randomised, double-blind, placebo-controlled, parallel Group, 52 week study.	133	Patients ≥ 18 and ≤ 80 years with T2DM, an HbA1c >7.0% and ≤10.0% and severe chronic renal insufficiency (GFR <30 ml/min).	Male patients: 60.2% Age (years, mean): 64.4	Linagliptin 5 mg/day with initial 12-week period of unchanged background antidiabetic therapy dosage followed by 40 weeks in which the dosages of the background antidiabetic therapy could be altered.	Change from baseline in HbA1c after 52 weeks of treatment. Superiority of linagliptin over placebo. Adjusted mean change: −0.72% (95% CI −1.03, −0.41; p < 0.0001)
1218.63*[33]	Phase III randomised, double-blind, placebo-controlled, parallel group 24 week multicentre study.	241	HbA1c ≥ 7.0% despite stable metformin and/or SU and/or insulin therapy; aged ≥ 70 years.	Male patients: 68.5%, Age (years, mean): 74.9	Linagliptin 5 mg/day with doses of background diabetes medications kept stable during screening, run-in and the first 12 weeks of randomised treatment, after which adjustments were permitted	Change from baseline HbA1c after 24 weeks. Superiority of linagliptin over placebo. Adjusted mean change: −0.64% (95% CI: −0.81, −0.48; p < 0.0001)

BMI: body mass index; CI: confidence interval; GFR: glomerular filtration rate; HbA1c: glycosylated haemoglobin; T2DM: type 2 diabetes mellitus
* Study not published