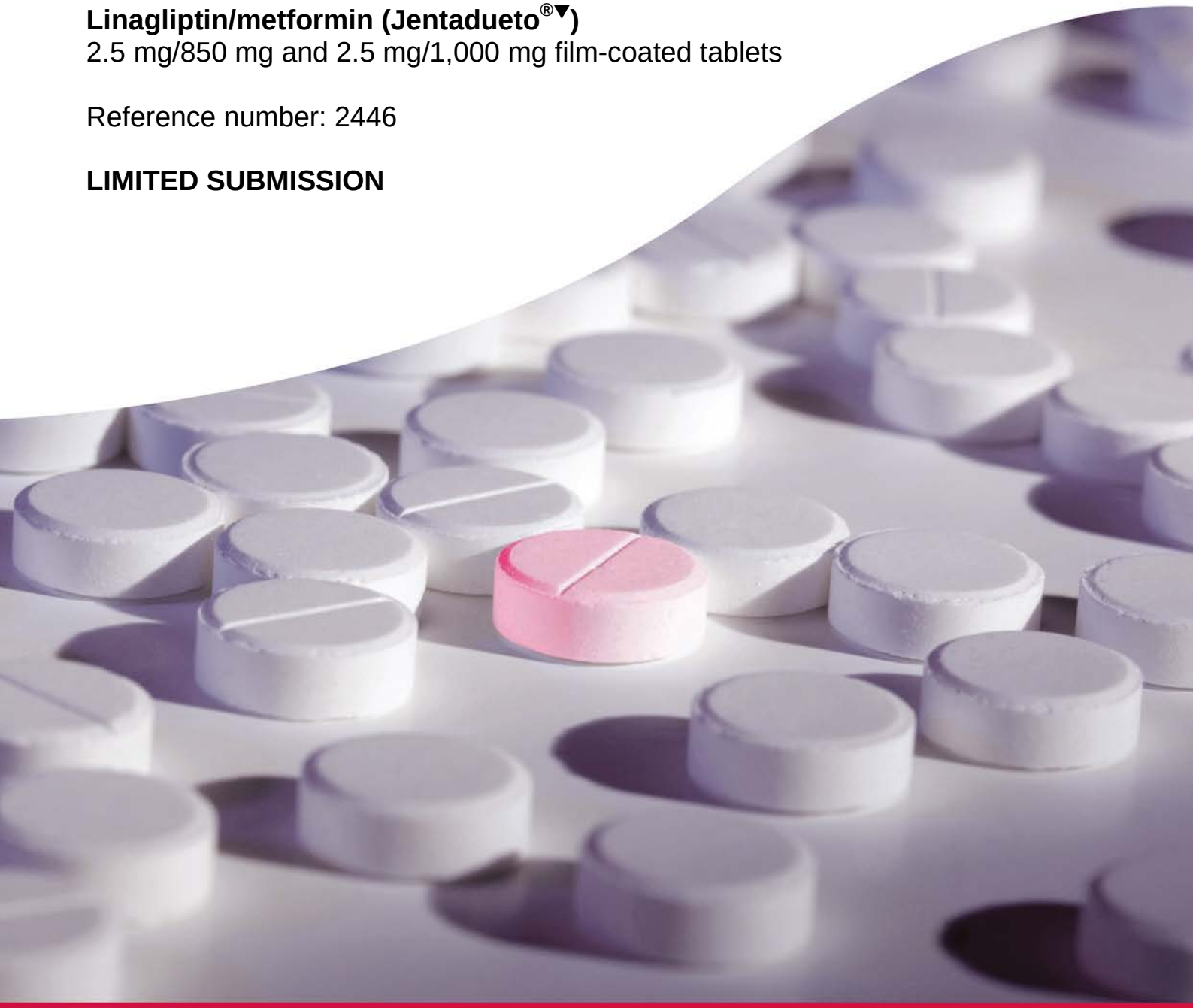
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Linagliptin/metformin (Jentadueto®▼)
2.5 mg/850 mg and 2.5 mg/1,000 mg film-coated tablets

Reference number: 2446

LIMITED SUBMISSION



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

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AWMSG Secretariat Assessment Report
Linagliptin/metformin (Jentadueto®▼)
2.5 mg/850 mg and 2.5 mg/1,000 mg film-coated tablets

This assessment report is based on evidence from a limited submission by Boehringer Ingelheim Ltd/Eli Lilly & Co Ltd on 26 March 2014[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Linagliptin/metformin (Jentadueto®▼) is indicated in the treatment of adult patients with type 2 diabetes mellitus in combination with insulin (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control when insulin and metformin alone do not provide adequate glycaemic control[2,3].
Dosing	The dose of antihyperglycaemic therapy with linagliptin/metformin should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability, while not exceeding the maximum recommended daily dose of 5 mg linagliptin plus 2,000 mg of metformin hydrochloride. Refer to the Summary of Product Characteristics for further information regarding linagliptin/metformin dosing[2,3].
Marketing authorisation date	Date of licence extension 24 January 2014[2,3] (licensed for the original indication on 20 July 2012[4]).
Comparators	The comparators included in the company submission were the individual components, linagliptin (Trajenta®▼) and metformin[1].
Limited submission details	Linagliptin/metformin (Jentadueto®▼) for the above indication met the following criteria for eligibility for a limited submission: • Anticipated usage in NHS Wales is considered to be of minimal budgetary impact. • Estimated small difference in cost compared to comparator(s).

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

2.1 Evidence of bioequivalence

The company submission provides evidence to demonstrate the bioequivalence of linagliptin/metformin (Jentadueto®▼) fixed dose combination with the individual components[1]. The evidence supplied included two phase I, randomised, single-dose, open-label, two-way crossover bioequivalence studies; each study enrolled 96 healthy volunteers[1,5]. Each volunteer received a single dose of the linagliptin/metformin fixed dose combination tablet (study 1288.3: 2.5 mg/850 mg; study 1288.1: 2.5 mg/1,000 mg) and the individual components, linagliptin plus metformin (study 1288.3: 2.5 mg plus 850 mg; study 1288.1: 2.5 mg plus 1,000 mg), separated by a washout period of at least 35 days[1,5].

For both studies, the geometric mean plasma concentration-time profiles were similar for the linagliptin/metformin fixed dose combination tablet and for the individual components[1,5]. Therefore, the fixed dose combination linagliptin/metformin 2.5 mg/850 mg and 2.5 mg/1,000 mg were found to be bioequivalent to single tablets of

linagliptin (2.5 mg) and metformin (850 mg and 1,000 mg, respectively) administered together[1,5].

The fixed dose combination tablets and the individual components were found to be well tolerated in the healthy volunteers with no evidence of any safety concerns[1,5]. However, the Summary of Product Characteristics (SPC) states that when linagliptin plus metformin is used in combination with insulin, a lower dose of insulin may be required to reduce the risk of hypoglycaemia[2,3].

2.2 Points to note

- Comparison of linagliptin/metformin (fixed dose combination) with the individual components of linagliptin plus metformin is outlined in phase I bioequivalence studies[1].
- In May 2013, the All Wales Medicines Strategy Group (AWMSG) recommended the use of linagliptin (Trajenta®▼) for the treatment of type 2 diabetes mellitus to improve glycaemic control in adults in combination with insulin with or without metformin, when this regimen alone, with diet and exercise, does not provide adequate glycaemic control[6]. Subsequently, in July 2013, AWMSG recommended the use of linagliptin/metformin (Jentadueto®▼) for the treatment of adult patients with type 2 diabetes mellitus: as an adjunct to diet and exercise to improve glycaemic control in adult patients inadequately controlled on their maximal tolerated dose of metformin alone, or those already being treated with the combination of linagliptin and metformin; and in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea[7].
- In their submission, the company also referred to clinical trial 1288.2; however, this trial did not study the licensed dose[1] and is therefore not discussed in this AWMSG Secretariat Assessment Report.

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The budget impact analysis presented by the applicant company included a comparison of the maximum annual costs associated with using linagliptin/metformin (fixed dose combination) and linagliptin and metformin as separate components for the treatment of adult patients with type 2 diabetes mellitus[1].

Using the Quality and Outcomes Framework Disease Register for Wales (2012–2013), the company estimate that there are 173,299 people in Wales suffering with diabetes mellitus[8], of which approximately 90% (156,000) have type 2 diabetes[9]. Based on company data, there are approximately 2,233 patients receiving fixed dose combination dipeptidyl-peptidase 4s (DPP-4; Janumet®, Komboglyze®, Eucreas® and Jentadueto®▼) and approximately 988 patients receiving combination treatment of metformin, DPP-4 and insulin[1]. The company note that the majority of these patients would be expected to receive the individual free dosing components, not the fixed dose combination. Therefore, the company expect the number of patients who would receive linagliptin/metformin (fixed dose combination) and insulin to be very low but the company have not provided the anticipated number of patients[1].

The company estimates of cost per patient are based on the assumption that linagliptin/metformin (fixed dose combination) would substitute linagliptin and metformin prescribed as separate components. Linagliptin/metformin (fixed dose combination) twice daily is priced at parity with linagliptin once daily, effectively meaning metformin (850 mg and 1,000 mg) is included at no additional cost. The estimated cost of treatment with linagliptin/metformin (fixed dose combination) is £434 per patient per

year[1]. Treatment with linagliptin and metformin as separate components would cost £451.30 per patient per year. The annual saving per patient is £17.30 but the budget impact cannot be calculated as the predicted number of patients receiving the fixed dose combination has not been included in the company submission.

3.1.1 AWTTC critique

- The number of patients receiving a combination treatment of metformin, DPP-4 and insulin was derived from company data on file and therefore cannot be verified by AWTTC.
- The company did not estimate the number of patients who would receive linagliptin/metformin as a fixed dose combination with insulin therefore only the cost per patient was reported and the budget impact cannot be calculated.

3.2 Comparative unit costs

Table 1 provides comparative annual acquisition costs of linagliptin/metformin 2.5 mg/850 mg to 2.5 mg/1,000 mg film-coated tablets and the comparators suggested by the company[1].

Table 1. Examples of annual costs for linagliptin/metformin fixed dose combination and fixed dose combination comparators for the treatment of type 2 diabetes in combination with insulin.

Medicine	Example regimen*	Annual cost†
Linagliptin/metformin (Jentadueto®▼) 2.5 mg/850 mg film-coated tablet 2.5 mg/1,000 mg film-coated tablet	2.5 mg/850 mg to 2.5 mg/1,000 mg twice daily	£433.57
Sitagliptin/metformin (Janumet®) 50 mg/1,000 mg film-coated tablet	50 mg/1,000 mg twice daily	£433.57
Saxagliptin/metformin (Komboglyze®) 2.5 mg/850 mg film-coated tablet 2.5 mg/1,000 mg film-coated tablet	2.5 mg/850 mg to 2.5 mg/1,000 mg twice daily	£411.93
Vildagliptin/metformin (Eucreas®) 50 mg/1,000 mg film-coated tablet	50 mg/1,000 mg twice daily	£413.42

* Regimen based on SPC dosing instructions[2,3,10–12]
† Costs are based on British National Formulary and Drug Tariff dosing instructions[13,14]

This table does not imply therapeutic equivalence of medicines or the stated doses
Refer to the SPCs for full dosing details[2,3,10–12]

4.0 ADDITIONAL INFORMATION

4.1 Prescribing and supply

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

The company do not anticipate that linagliptin/metformin (Jentadueto®▼) will be supplied by a home healthcare provider.

4.2 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

4.3 Evidence search

Date of evidence search: 22 April 2014.
Date range of evidence search: No date limits were applied to database searches.

REFERENCES

1 Boehringer Ingelheim Ltd, Eli Lilly & Co Ltd. Form C: Limited appraisal submission. Linagliptin/metformin (Jentadueto®▼). Mar 2014.

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Appendix: Previous AWMSG secretariat assessment report (published April 2013)

In April 2013, AWMSG appraised linagliptin/metformin (Jentadueto®) for the treatment of adult patients with type 2 diabetes mellitus:

- as an adjunct to diet and exercise to improve glycaemic control in adult patients inadequately controlled on their maximal tolerated dose of metformin alone, or those already being treated with the combination of linagliptin and metformin; and
- in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea (AWTTC reference number 1681).

This advice is now incorporated into the Final Appraisal Recommendation (FAR) of linagliptin/metformin (Jentadueto®) for the treatment of adult patients with type 2 diabetes mellitus in combination with insulin (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control when insulin and metformin alone do not provide adequate glycaemic control (AWTTC reference number 2446).

The original report for AWTTC reference number 1681 is included below for completeness.

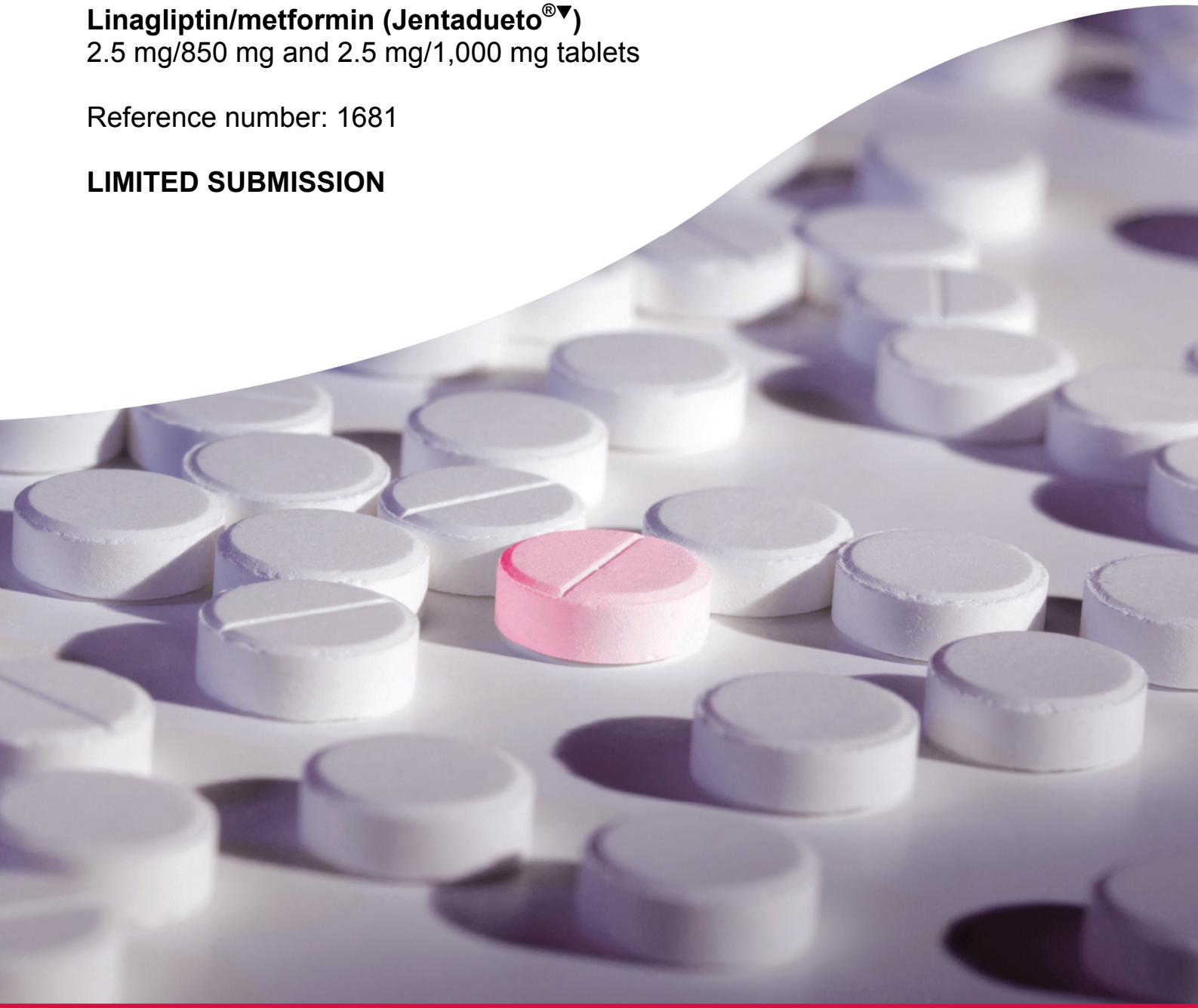
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Linagliptin/metformin (Jentadueto®▼)
2.5 mg/850 mg and 2.5 mg/1,000 mg tablets

Reference number: 1681

LIMITED SUBMISSION



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

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All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Appraisal reference number: 1681. Linagliptin/metformin (Jentadueto®▼) 2.5 mg/850 mg and 2.5 mg/1,000 mg tablets. April 2013.

AWMSG Secretariat Assessment Report
Linagliptin/metformin (Jentadueto®▼)
2.5 mg/850 mg and 2.5 mg/1,000 mg tablets

This assessment report is based on evidence from a limited submission by Boehringer Ingelheim/Eli Lilly & Co Ltd on 1 October 2012[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Linagliptin/metformin (Jentadueto®▼) is indicated in the treatment of adult patients with type 2 diabetes mellitus: as an adjunct to diet and exercise to improve glycaemic control in adult patients inadequately controlled on their maximal tolerated dose of metformin alone, or those already being treated with the combination of linagliptin and metformin; and in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea[2,3].
Marketing authorisation date	20 July 2012[2,3]
UK launch date	19 September 2012[1]
Comparators	The comparators requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) were the individual components, linagliptin (Trajenta®▼) and metformin.
Limited submission details	Linagliptin/metformin (Jentadueto®▼) for the above indication met the following criteria for eligibility for a limited submission: • New formulation with a pro-rata or lower cost per treatment. • Anticipated usage in NHS Wales is considered to be of minimal budgetary impact.

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

2.1 Evidence of bioequivalence

The company submission aims to demonstrate bioequivalence of linagliptin/metformin (Jentadueto®▼) fixed dose combination with the individual components. The evidence supplied included two randomised, single-dose, open-label, two-way crossover bioequivalence trials; each trial enrolled 96 healthy volunteers[1,4]. Each volunteer received a single dose of the linagliptin/metformin fixed dose combination tablet (study 1288.3: 2.5 mg/850 mg; study 1288.1: 2.5 mg/1,000 mg) and the individual components, linagliptin plus metformin (study 1288.3: 2.5 mg plus 850 mg; study 1288.1: 2.5 mg plus 1,000 mg), separated by a washout period of at least 35 days[1,4].

For both trials, the geometric mean plasma concentration-time profiles were similar for the linagliptin/metformin fixed dose combination tablet and for the individual components. Therefore, the fixed dose combination linagliptin/metformin

2.5 mg/850 mg and 2.5 mg/1,000 mg were found to be bioequivalent to single tablets of linagliptin (2.5 mg) and metformin (850 mg and 1,000 mg, respectively) administered together[4].

The fixed dose combination tablets and the individual components were found to be well tolerated in the healthy volunteers with no evidence of any safety concerns[1]. However, the Summary of Product Characteristics (SPC) states that when linagliptin plus metformin is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be required to reduce the risk of hypoglycaemia[2,3].

2.2 Points to note

- Comparison of linagliptin/metformin (fixed dose combination) with the individual components of linagliptin plus metformin is outlined in phase I bioequivalence studies[1]; no head to head evidence for clinical outcomes or safety has been included. Although the bioequivalence trials were conducted in healthy volunteers, it was considered to be acceptable by the European Medicines Agency (EMA)[5].
- The SPC states that linagliptin/metformin should be administered twice daily[2,3]; however, only a single dose of linagliptin/metfomin was received throughout the bioequivalence studies[1].
- In addition to the evidence outlined in Section 2.1, the company submission also referred to clinical trials which, either did not study the fixed dose formulation or did not study the licensed dose. Therefore, these studies were not included[1].
- In March 2013, AWMSG advised Welsh Government that linagliptin (Trajenta®▼) should be recommended as an option for use for the treatment of type 2 diabetes mellitus to improve glycaemic control[6]. This advice is awaiting Ministerial ratification.

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The budget impact analysis presented by the applicant company[1] includes a simple comparison of the maximum annual costs associated with using linagliptin/metformin (Jentadueto®▼) and linagliptin and metformin as separate components for the treatment of adult patients with type 2 diabetes mellitus.

Using the Quality and Outcomes Framework Disease Register for Wales (2010–2011)[7], the company estimated that there are 145,000 patients with type 2 diabetes. The company assumes that in 40% of these patients, diabetes is not controlled by diet and exercise alone, by metformin monotherapy, or by the addition of a sulphonylurea[1]. Based on company data, only a fraction of those patients in Wales that are treated with a dipeptidyl peptidase (DPP-4) inhibitor (such as linagliptin; either as a dual therapy in combination with metformin or as a triple therapy in combination with metformin and a sulphonylurea) currently use fixed dose combinations of a DPP-4 inhibitor and metformin. The company estimate that approximately 150 patients in Wales use Janumet® (sitagliptin/metformin), which is the most commonly prescribed fixed-dose DPP-4 inhibitor/metformin combination product[1].

The company's estimates of budget impact are based on the assumption that Jentadueto®▼ would substitute linagliptin and metformin prescribed as separate components. Jentadueto®▼ twice daily is priced at parity with linagliptin (Trajenta®▼) once daily, effectively meaning metformin (850 mg and 1,000 mg) is included at no additional cost. The estimated cost of treatment with Jentadueto®▼ is £434 per patient per year[1]. Treatment with linagliptin and metformin as individual components would cost £450.82 per patient per year (assuming linagliptin 5 mg once daily and metformin

850 mg twice daily), and £458.51 (assuming linagliptin 5 mg once daily and metformin 1,000 mg twice daily)[8].

3.2 AWTTC critique of the budget impact analysis

- The company assumes Jentadueto®▼ will displace only linagliptin and metformin as separate components, in line with its licensed indication. Other fixed dose formulations of DPP-4 inhibitor and metformin (e.g. Janumet® [sitagliptin plus metformin] and Eucreas® [vildagliptin plus metformin]) are not assumed to be relevant alternatives.
- The company has not attempted to estimate uptake of Jentadueto®▼, instead suggesting that uptake will be low based on that observed for Janumet® (sitagliptin plus metformin).

3.3 Table of comparative unit costs

Table 1 provides examples of comparative annual acquisition costs for oral hypoglycaemic products used in combination with metformin and as separate components, for the treatment of adult patients with type 2 diabetes mellitus.

Table 1 Example comparative annual drug acquisition costs for the treatment of adult patients with type 2 diabetes mellitus.

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 or 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 50mg/metformin 1,000 mg) tablets	50 mg/ 1,000 mg twice daily	451
Galvus® (vildagliptin) 50 mg tablets	50 mg twice daily	414
Eucreas® (vildagliptin 50 mg/metformin 850 mg), Eucreas® (vildagliptin 50mg/metformin 1,000 mg) tablets	50 mg/850 mg twice daily to 50 mg/1,000 mg twice daily	413
Actos® (pioglitazone) 15 mg, 30 mg and 45 mg tablets	15 mg to 45 mg once daily	337 to 516
Competact® (pioglitazone 15 mg/metformin 850 mg) tablets	15 mg/850 mg twice daily	468
Onglyza® (saxagliptin) 2.5 mg and 5 mg tablets	5 mg daily	412
Glucophage® (metformin) 500 mg and 850 mg tablets	500 mg to 850 mg two or three times daily	25 to 63
See relevant SPCs[2,3,9–17] for full dosing details. Costs are based on MIMS[8] list prices as of 07/01/2013. This table does not imply therapeutic equivalence of drugs or the stated doses.		

4.0 ADDITIONAL INFORMATION

4.1 Appropriate place for prescribing

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

4.2 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).

4.3 Evidence search
Date of evidence search: 5 and 6 December 2012
Date range of evidence search: No date limits were applied to database searches.

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