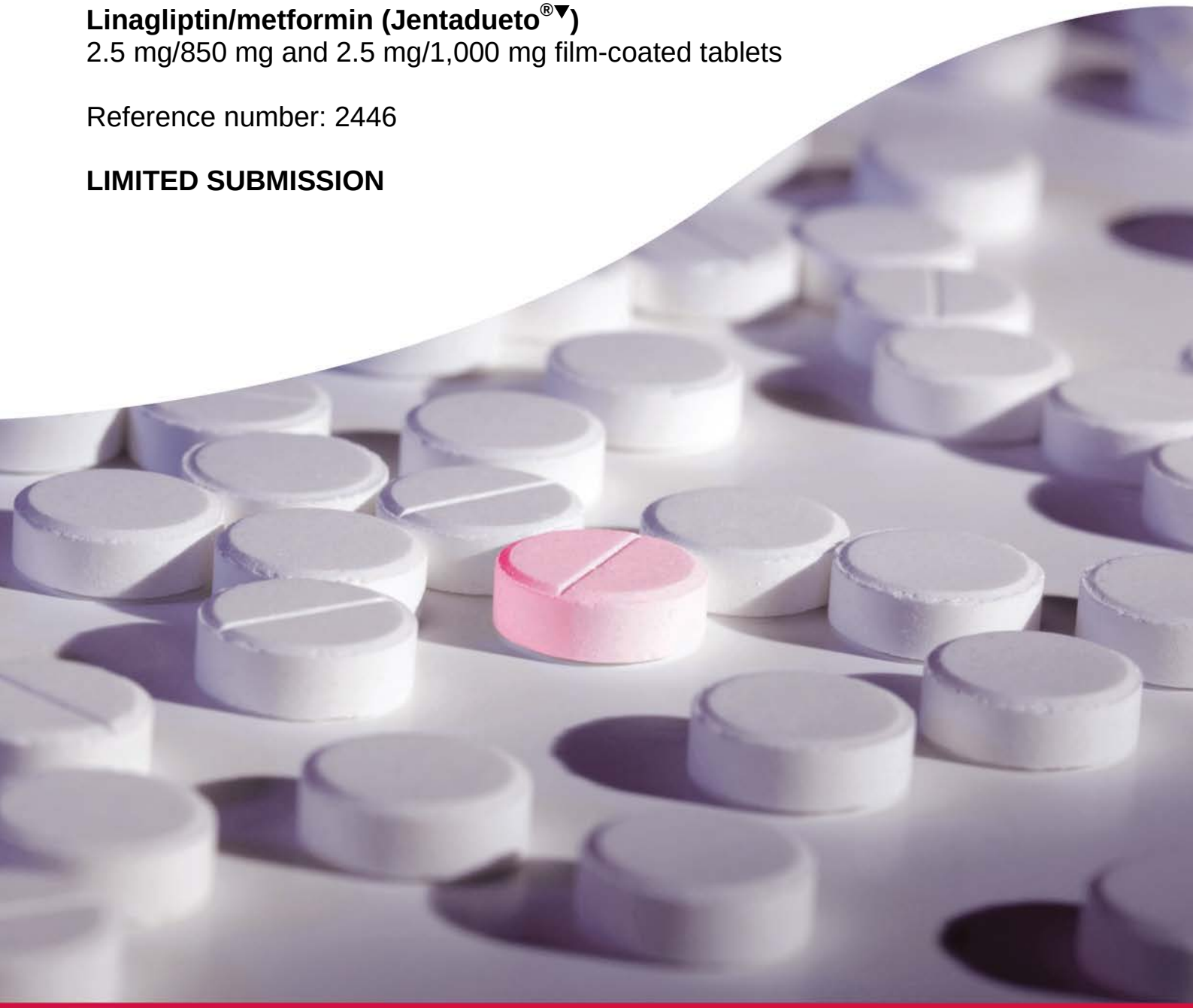
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

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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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

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