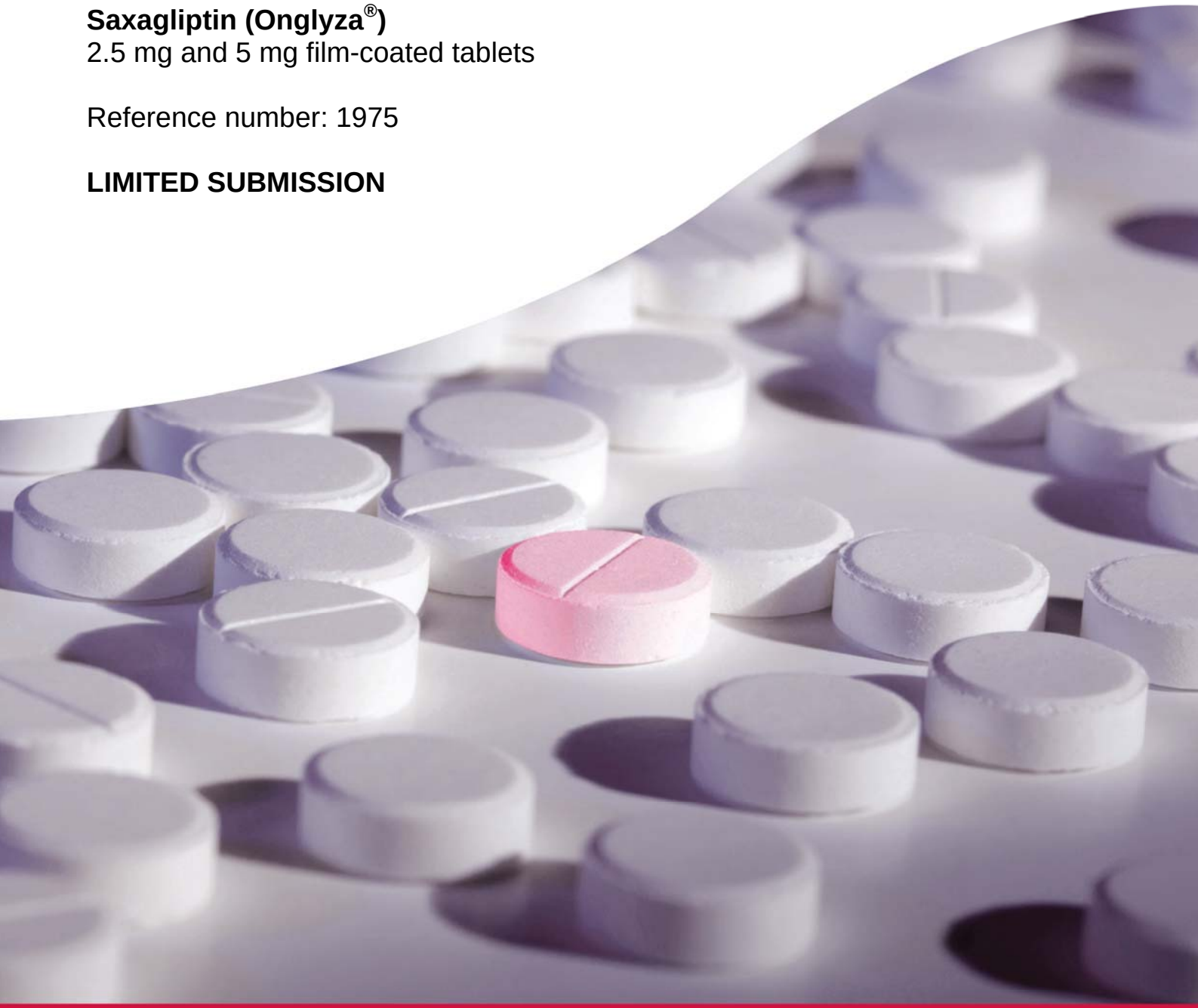
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Saxagliptin (Onglyza®)
2.5 mg and 5 mg film-coated tablets

Reference number: 1975

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
Saxagliptin (Onglyza®) 2.5 mg and 5 mg film-coated tablets

This assessment report is based on evidence from a limited submission by AstraZeneca UK Ltd/Bristol-Myers Squibb Pharmaceuticals Ltd on 11 July 2013[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Saxagliptin (Onglyza®) is indicated in adult patients aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as triple oral therapy in combination with metformin plus a sulphonylurea when this regimen alone, with diet and exercise, does not provide adequate glycaemic control[2].
Marketing authorisation date	18 February 2013 (5 mg film-coated tablets licensed as a dual oral therapy on 1 October 2009)[2,3].
Comparators	The comparators included in the company submission were sitagliptin (Januvia®) and linagliptin (Trajenta®▼)[1].
Limited submission details	Saxagliptin (Onglyza®) for the above indication met the following criteria for eligibility for a limited submission: • A minor licence extension. • 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

The company provided an indirect treatment comparison (ITC) of three randomised controlled trials identified from a systematic review of third-line pharmacotherapies in adults with type 2 diabetes mellitus (T2DM) experiencing inadequate glycaemic control on metformin and a sulfonylurea, performed by the Canadian Agency for Drugs and Technologies in Health (CADTH)[1].

2.1 Indirect treatment comparison

The studies included were all phase III, multinational, multicentre, randomised, double-blind, placebo-controlled, parallel-group studies. NCT01128153 (n = 257), NCT00106704 (stratum 2*: n = 229) and NCT00602472 (n = 1,058) investigated the dipeptidyl peptidase-4 (DPP-4) inhibitors, saxagliptin (Onglyza®), sitagliptin (Januvia®) and linagliptin (Trajenta®▼), respectively, versus placebo for adults with T2DM and inadequately controlled glycaemic levels despite combination therapy of metformin plus a sulfonylurea in addition to diet and exercise. No relevant head-to-head trials were identified in the CADTH systematic review[1,4–7].

The adjusted ITC was conducted utilising methodology reported by Bucher et al[8]. Mean change in glycosylated haemoglobin (HbA1c) level from baseline to week 24 (the end of follow up in each trial) was the primary efficacy outcome for all three trials and was therefore the selected efficacy measure for the adjusted ITC (see Table 1). The selected safety measure was the odds ratio of a patient-reported hypoglycaemic event

* Stratum 2 was sitagliptin or placebo with metformin and sulfonylurea; stratum 1 was sitagliptin or placebo with sulfonylurea only and has therefore not been included in the ITC.

(including overall events and severe events) occurring during the 24 weeks of treatment. In addition, weight gain, overall adverse events (AEs), overall serious AEs (SAEs) and discontinuation due to AEs were assessed[1].

Table 1. Change in HbA1c at week 24 for NCT01128153, NCT00106704 (stratum 2) and NCT00602472[4–6].

Study	Study arm (+ metformin + sulfonylurea)	Adjusted mean change from baseline in HbA1c at week 24 % (95% CI)	Difference % (95% CI)
NCT01128153	Saxagliptin (n = 127)	−0.74 [Commercial in confidence data removed]	[Commercial in confidence data removed]
	Placebo (n = 127)	−0.08 [Commercial in confidence data removed]	
NCT00106704 (stratum 2)	Sitagliptin (n = 115)	−0.59 (−0.74 to −0.44)	−0.89 (−1.10 to −0.68; p < 0.001)
	Placebo (n = 105–109)	0.30 (0.14 to 0.45)	
NCT00602472	Linagliptin (n = 778)	−0.72 (95% CI not provided)	−0.62 (−0.73 to −0.50; p < 0.0001)
	Placebo (n = 262)	−0.10 (95% CI not provided)	
CI: confidence interval			

[Commercial in confidence data removed]

At the time of licensing, the Committee for Medicinal Products for Human Use (CHMP) concluded from the results of study NCT01128153 that the safety profile of saxagliptin was comparable to that of placebo, and that there were no unexpected AEs[9].

2.1 Points to note

- There are no relevant direct head-to-head studies for the comparison of saxagliptin, sitagliptin and linagliptin for the indication under consideration and therefore the company have performed an adjusted ITC. The studies included in the ITC were of similar design and recruited patients with similar baseline characteristics; however, ITCs are at greater risk of bias than head-to-head randomised comparisons and results should therefore be interpreted with caution.
- Due to the relatively short duration of the studies described, it is not possible to determine whether there are differences in the long-term health outcomes or safety profiles (including rate of hypoglycaemic events) of saxagliptin, sitagliptin or linagliptin.
- The company has not provided a comparison to vildagliptin (Galvus®). However, in February 2013, the All Wales Medicines Strategy Group (AWMSG) issued a Statement of Advice which states that in the absence of a submission from the holder of the marketing athorisation, vildagliptin (Galvus®) cannot be endorsed for use within NHS Wales for the treatment of T2DM in adults as triple oral therapy in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control; or in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control[10].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The budget impact evidence presented by the company includes a comparison of the maximum annual costs associated with the use of saxagliptin versus sitagliptin or linagliptin, as part of triple oral therapy for patients with T2DM. The applicant company utilised NHS Wales Quality and Outcomes Framework data and Welsh prevalence estimates from Diabetes UK to establish the number of T2DM patients in Wales[11,12]. 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. The number of patients currently prescribed a DPP-4 inhibitor as part of a triple therapy regimen was subsequently estimated using company-acquired UK patient data[13]. The company reported the five year budget impact of treating patients with saxaglitpin versus sitaglitpin/linaglitpin, based on 100% uptake (see Table 2).

Table 2. Company-reported five-year budget impact of saxagliptin versus sitagliptin/linagliptin[14]

	Year 1 (2013)	Year 2 (2014)	Year 3 (2015)	Year 4 (2016)	Year 5 (2017)
Number of eligible triple therapy patients	6,011	6,276	6,552	6,840	7,141
Cost of saxagliptin per year	£2,476,168	£2,585,119	£2,698,864	£2,817,615	£2,941,590
Displaced costs of sitagliptin and linagliptin	£2,606,245	£2,720,920	£2,840,640	£2,965,628	£3,096,116
Maximum total net costs	-£130,077	-£135,801	-£141,776	-£148,014	-£154,527

3.2 AWTTC critique of the budget impact analysis

- The company-reported budget impact calculations are based upon 100% uptake figures, which is unlikely to reflect clinical practice and may result in an overestimation of net budget impact.
- The company has assumed that only patients currently receiving sitagliptin or linagliptin (as single or combination products) may be switched to saxagliptin. Vildagliptin has not been considered; however, it should be noted that AWMSG has issued a Statement of Advice for vildagliptin (see Section 2.1).

3.3 Comparative unit costs

Table 3. Example comparative annual acquisition costs for DPP-4 inhibitors

Medicine	Example regimen	Cost per patient per year*
Saxagliptin (Onglyza®) 2.5 mg and 5 mg film-coated tablets	5 mg once-daily	£412
Sitagliptin (Januvia®) 25 mg, 50 mg and 100 mg film-coated tablets	100 mg once-daily	£434
Linagliptin (Trajenta®▼) 5 mg film-coated tablets	5 mg once-daily	£434
Vildagliptin (Galvus®) 50 mg tablets	50 mg twice-daily	£414
*Costs are based on Monthly Index of Medical Specialities (MIMS) list prices as of July 2013[15]. This table does not imply therapeutic equivalence of medicines or the stated doses. Refer to the summary of product characteristics (SPCs) for full dosing details[2,16–18].		

4.0 ADDITIONAL INFORMATION

4.1 Prescribing and supply

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

The company do not anticipate that saxagliptin (Onglyza®) 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 Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

4.3 Evidence search

Date of evidence search: 26 July 2013
Date range of evidence search: No date limits were applied to database searches.

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