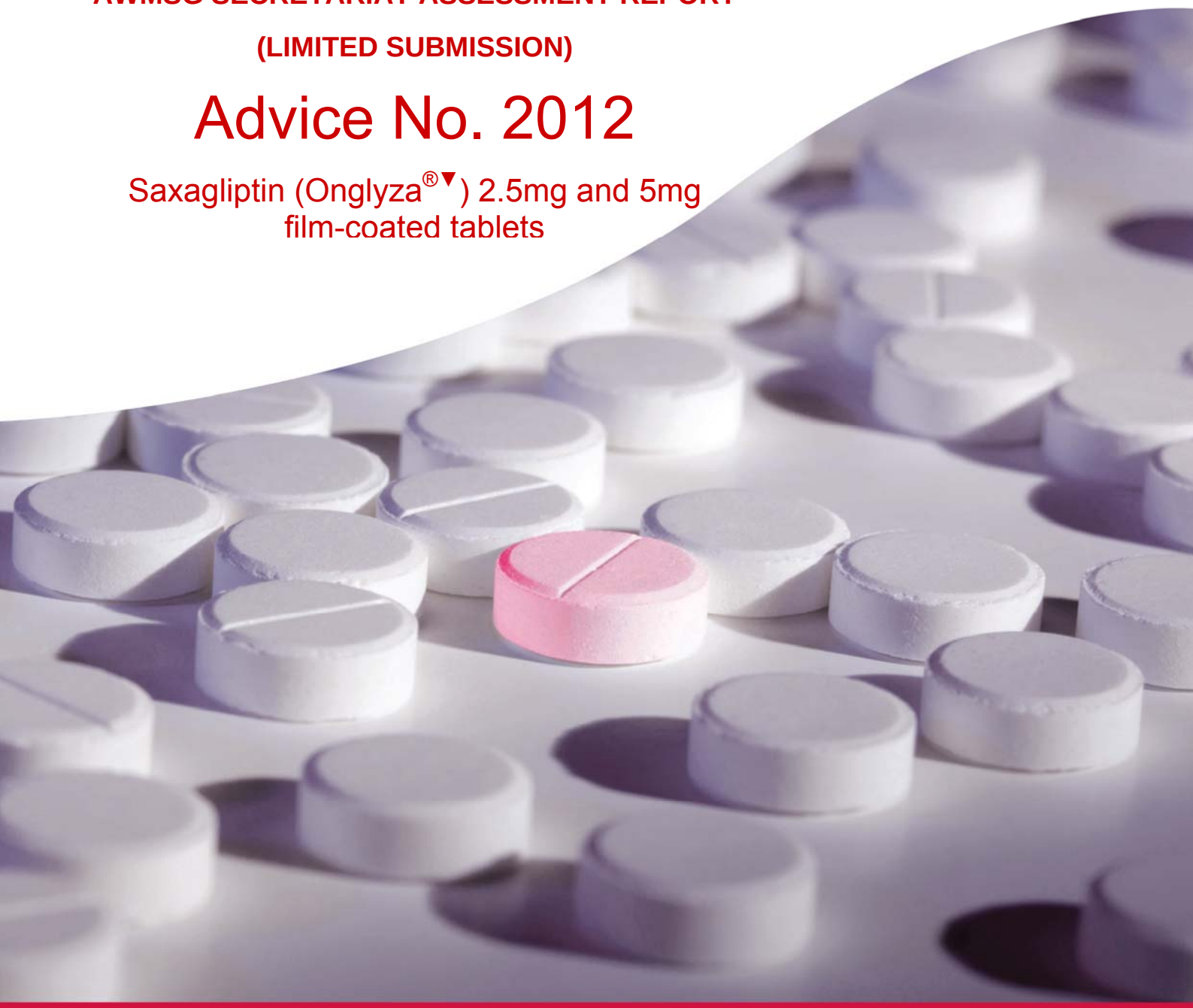
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(LIMITED SUBMISSION)

Advice No. 2012

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



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

AWMSG Secretariat Assessment Report – Advice No. 2012
Saxagliptin (Onglyza®▼) 2.5 mg and 5 mg film-coated tablets

This assessment report is based on evidence from a limited submission by Bristol Myers Squibb Pharmaceuticals / AstraZeneca EEIG on 23 February 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	The licence extension under consideration is: Saxagliptin (Onglyza®▼) for 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[2].
Dosing	The recommended dose is 5 mg once daily as add-on combination therapy with insulin (with or without metformin). Refer to the Summary of Product Characteristics (SPC) for further information regarding dosing for specific conditions and patient type[2].
Marketing authorisation date	22 November 2011[3] (licensed for original indication on 1 October 2009)[2].

2.0 DECISION CONTEXT

2.1 Background

Approximately 85% of people with diabetes have type 2 diabetes mellitus (T2DM), which is caused by insufficient insulin production by pancreas beta-cells, or the inability of the body to properly utilise endogenous insulin[4]. T2DM is associated with increased cardiovascular risk and microvascular complications such as eye, nerve, and renal damage[5]. Saxagliptin 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[1].

Based on company market research data, the number of people with T2DM in Wales is estimated at 117,684, and the applicant company estimates that saxagliptin as an add-on to insulin will be used to treat a total of 27 patients each year in Wales[1].

2.2 Comparators

The comparators requested by the Welsh Medicines Partnership (WMP)* were:

- Sitagliptin (Januvia®▼)
- Pioglitazone

Pioglitazone is licensed for use with insulin and with metformin, as dual therapies, but is not specifically licensed for use as a triple therapy with metformin and insulin[6], in contrast to saxagliptin[2] and sitagliptin[7].

*In April 2012 the Welsh Medicines Partnership became part of the All Wales Therapeutics and Toxicology Centre (AWTTC).

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. May 2009[5].
- Scottish Intercollegiate Guidelines Network. Management of diabetes. Guideline 116. March 2010[8].
- The All Wales Medicines Strategy Group (AWMSG) has previously issued the following recommendation:
  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[9].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

3.1 Saxagliptin as add-on to insulin (with or without metformin) compared to placebo

The company submission included a randomised, double-blind, multi-centre, placebo-controlled phase III study carried out with saxagliptin 5 mg as add-on therapy to insulin monotherapy or insulin plus metformin. Prior to saxagliptin or placebo treatment patients were given a four week dietary and exercise lead in period during which they remained on insulin and metformin (if applicable) according to their current regimen. Patients on stable baseline therapy of insulin ± metformin for at least eight weeks were stratified by metformin use and randomised 2:1 to saxagliptin or placebo respectively. Patients who completed a 24 week short term stable treatment period, and patients who met the rescue criteria (i.e. patients having their insulin dose increased), were eligible to enter a double-blind, long term extension of a further 28 weeks[10].

The primary end point of adjusted mean change in HbA1c from baseline to week 24 (or rescue) was met (saxagliptin: −0.73% versus placebo: −0.32%; p<0.0001, n=304 and n=151 respectively)[10]. Similar HbA1c reductions versus placebo were achieved for the saxagliptin arm regardless of metformin use (−0.4% for both subgroups). Improvements from baseline HbA1c were sustained in the saxagliptin arm compared to the placebo arm, with or without metformin at Week 52. The HbA1c change for the saxagliptin group (n=244) was -0.75% compared to placebo (n=124) -0.38%: a difference of -0.37% at Week 52[1].

3.2 Saxagliptin as add-on to insulin (with or without metformin) compared to pioglitazone and sitagliptin

In the absence of trials directly comparing saxagliptin with either pioglitazone or sitagliptin in conjunction with insulin (with or without metformin), the company have provided a meta analysis of the effect of pioglitazone added to insulin compared to insulin alone[11] and a study comparing sitagliptin added to insulin compared to matching placebo[12]. Results for these studies are given in Table 1. Comparisons should be interpreted with caution due to differences in patient characteristics and study protocols.

Table 1. Key results from saxagliptin and sitagliptin clinical studies and pioglitazone meta-analysis as an add on to insulin (with or without metformin)

	Barnett et al[10] 2012 24 week data		Waugh et al[11] 2009 12-36 week meta-analysis data		Vilsboll et al[12] 2010 24 week data	
	Saxagliptin	**Placebo**	**Pioglitazone**	**No pioglitazone**	**Sitagliptin**	**Placebo**
Mean HbA1c change from baseline (%)	-0.73 (p<0.0001)	-0.32	-0.5 (p<0.0001)		-0.6 (p<0.001)	0.0
Mean change from baseline body weight (Kg)	0.39	0.18	1.4 to 4.4	−0.04 to 4.9	0.1	0.1
Hypoglycaemia (% of patients) or relative risk	18.4	19.9	Relative risk 1.30 (p=0.02)		16 (p=0.003)	8

The baseline HbA1c values were similar in the saxagliptin and sitagliptin studies (8.7%), but were variable in the pioglitazone studies (7.6% to 10%). The reductions in mean HbA1c observed for the three treatments compared to the placebo (or no pioglitazone) were 0.41 for saxagliptin, 0.5 for pioglitazone and 0.6 for sitagliptin.

3.3 Comparative safety

For saxagliptin the Committee for Medicinal Products for Human Use (CHMP) concluded that the incidence of adverse events (AEs), serious adverse events and AEs leading to discontinuation was similar between treatment groups and that most AEs were unlikely or unrelated to study drug treatment and were mild or moderate in intensity[13]. Table 1 shows a small increase in body weight in the saxagliptin and placebo arms (0.39 kg and 0.18 kg respectively) at week 24.

In most pioglitazone studies included in the meta-analysis, patients in the insulin plus pioglitazone groups gained more weight than patients in the insulin only groups (mean difference 2.91 kg, range 3.85 to −3.50 kg, no p-values were reported)[8]. For sitagliptin the small weight gain was comparable to that found with placebo treatment[12]. In contrast to saxagliptin, hypoglycaemia (or relative risk of) was significantly increased for patients receiving either pioglitazone or sitagliptin compared to those receiving no pioglitazone or placebo respectively.

The SPC for pioglitazone reports that there have been post-marketing cases of cardiac failure reported when used in combination with insulin or in patients with a history of cardiac failure[6].

3.4 AWTTC critique

- In the absence of head-to-head trials of saxagliptin with the comparators requested by AWTTC, comparisons should be interpreted with caution due to differences in patient characteristics and study protocols.
- Whilst CHMP conclude that overall the addition of saxagliptin to patients treated with insulin was effective, with similar results in patients with or without metformin use at baseline; they highlight that the effect was modest. This was expressed in the proportion of patients achieving therapeutic glycaemic response (HbA1c < 7%): 17.3% for the saxagliptin arm compared to 6.7% for the placebo arm[13]. Reductions in mean HbA1c observed for saxagliptin, sitagliptin and pioglitazone compared to placebo (or no pioglitazone) were similar.
- The incidence of hypoglycaemia was comparable in patients receiving saxagliptin versus those receiving placebo[10]. In contrast, pioglitazone[11] and

sitagliptin[12] caused statistically significant increases in hypoglycaemia relative to insulin alone and placebo with insulin respectively.

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

Diabetes UK reported a 5.0% prevalence of diabetes in Wales in 2011, equivalent to around 160,533 people[14]. Based on company market research data, the number of people with T2DM is estimated at 117,684, of which 186 are estimated to use insulin plus either sitagliptin or pioglitazone, and 464 are estimated to use insulin plus metformin plus either sitagliptin or pioglitazone. Based on the assumption that saxagliptin will achieve 6.6% of the market for insulin plus either sitagliptin or pioglitazone, and 2.7% of the market for insulin plus metformin plus either sitagliptin or pioglitazone, the company estimates that saxagliptin as an add-on to insulin will be used to treat a total of 27 patients each year in Wales. This level of use is assumed to remain constant in each of years 1 to 5.

5.1.2 Results of company's budget impact analysis

The company anticipates cost savings from the use of saxagliptin 5 mg once daily instead of pioglitazone (assumed dose 30 mg daily) and sitagliptin 100 mg once daily, based on its lower acquisition costs.

5.1.3 AWTTC critique of the company's budget impact estimates

It is unclear if the company's estimates of the numbers of patients eligible for treatment with saxagliptin as add-on therapy to insulin are accurate or reliable; however, the current acquisition cost of saxagliptin is currently lower than either sitagliptin or pioglitazone.

5.2 Comparative unit costs

Table 2 shows example annual acquisition costs for saxagliptin and the main comparators when used as add-on to insulin therapy in adults with T2DM.

Table 2. Example acquisition costs for saxagliptin, sitagliptin and pioglitazone

Oral regimen in combination with insulin	Example doses	Annual cost per patient
Dual therapy (oral agent plus insulin)		
Onglyza®▼ (saxagliptin)* 5 mg tablets	5 mg once daily	£412
Januvia®▼ (sitagliptin)* 100 mg tablets	100 mg once daily	£434
Actos® (pioglitazone) 15 mg, 30 mg and 40 mg tablets	15–30 mg once daily increased to 45 mg once daily according to response	£337-£516
Pioglitazone (Non-proprietary) 15 mg, 30 mg and 45mg tablets	15–30 mg once daily increased to 45 mg once daily according to response	£314-£481
Triple therapy (oral agent plus metformin plus insulin)		
Onglyza®▼ (saxagliptin)* 5 mg tablets + non-proprietary metformin 500 mg tablets	Saxagliptin 5 mg once daily + metformin 1,000 mg twice daily	£435
Januvia®▼ (sitagliptin)* 100 mg tablets+ non-proprietary metformin 500 mg tablets	Sitagliptin 100 mg once daily + metformin 1,000 mg twice daily	£457
Janumet®▼ (sitagliptin 50 mg/metformin 1,000 mg) tablets	One 50 mg/1,000 mg tablet twice daily	£451
Costs are based on MIMS[15] and eDrug Tariff[16] list prices as of 19th March 2012. **Saxagliptin[2] and sitagliptin[7] may be used as add-on to insulin with or without metformin. Pioglitazone is not specifically licensed for use in combination with both metformin and insulin[6]. See relevant Summaries of Product Characteristics for full dosing details.* *This table does not imply therapeutic equivalence of drugs or the stated doses.*		

6.0 ADDITIONAL INFORMATION

6.1 Shared care arrangements

AWTTC is of the opinion that saxagliptin is appropriate for prescribing by all prescribers within NHS Wales for the above indication.

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: 14 March 2012
Date range of evidence search: No date limits were applied to database searches.

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