AWMSG Secretariat Assessment Report – Advice no. 2011
Saxagliptin (Onglyza®▼) 2.5 mg tablets

This assessment report is based on evidence from a limited submission by Bristol Myers Squibb/AstraZeneca EEIG on 8 August 2011.

1.0 PRODUCT 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: • in combination with metformin, when metformin alone, with diet and exercise, does not provide adequate glycaemic control; • in combination with a sulphonylurea, when the sulphonylurea alone, with diet and exercise, does not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate; • in combination with a thiazolidinedione, when the thiazolidinedione alone with diet and exercise, does not provide adequate glycaemic control in patients for whom use of a thiazolidinedione is considered appropriate[1]. This assessment report concerns a licence extension for the use of saxagliptin 2.5 mg in patients with moderate or severe renal impairment[2].
Dosing	The recommended dose of saxagliptin in patients with moderate to severe renal impairment is 2.5 mg once daily as add-on therapy, with or without food at any time of the day. The recommended dose of saxagliptin for the original indication is 5 mg[1]. Assessment of renal function is recommended prior to initiation of saxagliptin treatment, and patients should be monitored periodically thereafter. Saxagliptin is not recommended for patients with end-stage renal disease (ESRD) requiring haemodialysis[1].
Marketing authorisation date	28 February 2011 (licensed for the original indication on 1 October 2009)[1].

2.0 DECISION CONTEXT

2.1 Background

The majority (approximately 85%) of people with diabetes have type 2 diabetes mellitus (T2DM). This is caused by insufficient insulin production by pancreas beta-cells, or the inability of the body to properly utilise endogenous insulin[3]. T2DM is associated with increased cardiovascular risk and microvascular complications such as eye, nerve, and renal damage[4]. Impaired renal function in T2DM patients may preclude the use of first line medicines such as metformin, in which case, alternative oral anti-diabetic agents should be considered[5,6].

There is no standard treatment regimen for T2DM patients with moderate to severe renal impairment, although pioglitazone[7] and immediate-release exenatide[8] may be considered suitable treatments. No dose adjustment is necessary for pioglitazone (Actos®▼) in patients with a creatinine clearance > 4 ml/min[7]. Exenatide (Byetta®▼) however is not recommended for use in severe renal impairment and should be used with caution in the elderly[8].

The company estimates that there are 153,175–206,040 patients in Wales with T2DM, of which 20–25% experience moderate to severe renal impairment. They further estimate that 245 renally impaired patients with T2DM are failing first line monotherapy and would be suitable to receive saxagliptin[2].

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. Other DPP4 inhibitors such as sitagliptin (Januvia®▼) and vildagliptin (Galvus®▼, Eucreas®▼) are not recommended in patients with moderate to severe renal impairment[9,10].

Saxagliptin 5 mg in combination with first line medicines (metformin, a sulphonylurea or thiazolidinedione) was previously licensed to treat T2DM patients with normal to mild renal impairment[1]. The licence extension presented in the company's limited submission proposes the use of saxagliptin 2.5 mg once daily as add-on therapy for the treatment of T2DM patients with moderate (creatinine clearance [CrCl] 30–50 mg/ml) to severe (CrCl < 30 mg/ml) renal impairment[2]. The dose adjustment was required to maintain optimum treatment conditions, as systemic exposure of saxagliptin 5 mg was increased in T2DM patients with significant renal dysfunction[11,12].

It is important to note that the original indication for saxagliptin 5 mg has not been appraised by the All Wales Medicines Strategy Group (AWMSG) or by the National Institute for Health and Clinical Excellence (NICE), and **only the licence extension presented herein is eligible for appraisal**.

2.2 Comparators

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

- Exenatide (Byetta®▼)
- Pioglitazone (Actos®▼)

The company suggest in their submission that the comparison of saxagliptin versus exenatide is inappropriate as they consider these medicines represent different lines of treatment (second line vs. third line, respectively). In addition, despite undertaking a literature search, the company could not identify any clinical evidence that would allow a useful comparison of the effectiveness of pioglitazone and saxagliptin in patients with moderate to severe renal impairment.

2.3 Guidance and related advice

- NICE. Type 2 diabetes: the management of type 2 diabetes. Clinical guideline 87. May 2009[4].
- Scottish Intercollegiate Guidelines Network. Management of diabetes. Guideline 116. March 2010[13].
- National Horizon Scanning Centre. Saxagliptin (BMS 477118) for type 2 diabetes. April 2008[14].
- Regional Drug and Therapeutics Centre. New drug evaluation: Saxagliptin. January 2010[15].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

In light of the lack of evidence allowing a comparison of the clinical effectiveness of saxagliptin with any comparator, the company have provided placebo-controlled clinical data in support of their submission[2].

3.1 The clinical effectiveness of saxagliptin in renally impaired patients with type 2 diabetes mellitus

The company submission included data from a randomised, multi-centre, parallel-group, double-blind, placebo-controlled phase III study that evaluated the clinical efficacy and tolerability of saxagliptin 2.5 mg in T2DM patients aged at least 18 years, with inadequate glycaemic control (HbA1c levels: 7–11%) and moderate, severe, or end-stage renal impairment[2,12]. End-stage renal disease will not be addressed hereafter as it is not part of the indication under appraisal. The study included a 2-week single-blind placebo lead-in period followed by a 52-week treatment period with saxagliptin 2.5 mg or placebo, randomised in a 1:1 ratio. See Table 1 for details of randomisation.

Table 1. Number of randomised patients that completed each treatment period in the saxagliptin 2.5 mg efficacy and safety study

	Patients randomised	Patients with renal impairment at baseline			Patients that completed 12-week period	Patients that completed 52-week period
		Moderate	Severe	End-stage		
Saxagliptin 2.5 mg	85	48	18	19	61	42
Placebo	85	42	23	20	68	50
Total	**170**	**90**	**41**	**39**	**129**	**92**
All figures taken from the European Public Assessment Report[5] and Nowicki 2011[12]						

Patients were allowed their stable dose of oral anti-diabetic drugs (OAD) and/or insulin during the first 12 weeks of the treatment period, and dose adjustments were permitted in the following 40 weeks. At baseline, insulin treatment was more common in the saxagliptin group (83.5% vs. 67.1%), whereas use of OADs was more common in the placebo group (27.1% vs. 35.3%). No patients received metformin and the most commonly used OADs in both treatment arms were sulphonylureas. The average age of the total population was 67 years, and 31 (18.2%) patients were aged at least 75 years[12].

The primary efficacy endpoint was the absolute change in glycosylated haemoglobin (HbA1c) from baseline at week 12 (ref. 10). Secondary endpoints were the change in HbA1c from baseline at week 52, the proportion of patients experiencing a ≥ 0.5% decrease in HbA1c at week 12, and change in background anti-hyperglycaemic therapy from baseline at week 52. Using the last-observation-carried-forward (LOCF) imputation method in the intent-to-treat (ITT) population, the adjusted mean change of HbA1c from baseline at week 12 for saxagliptin (−0.86%, 95% confidence interval [CI] −1.08 to −0.64) compared to placebo (−0.44%, 95% CI −0.66 to −0.23) was significantly different (p = 0.007). However, in each renal impairment group, there was a non-significant but numerically larger mean reduction in HbA1c in response to saxagliptin compared to placebo (moderate: −0.64% [95% CI −0.9 to −0.37] vs. −0.05% [95% CI −0.33 to 0.22]; severe: −0.95% [95% CI −1.41 to −0.49] vs. −0.5% [95% CI −0.9 to −0.09]).

There were significantly more patients achieving ≥ 0.5% reduction in HbA1c at week 12 in response to saxagliptin in comparison to placebo (85.2% vs. 62.7%, p = 0.001)[12]. It was also reported that 33.3% of patients in the saxagliptin group achieved a HbA1c level < 7%, in contrast to 24.1% in the placebo group[5]. The adjusted mean in HbA1c levels from baseline at week 52 in the total population was also significantly reduced in response to saxagliptin in comparison to placebo (-1.08 [95% CI −1.37 to −0.8] vs. −0.36 [95% CI −0.63 to −0.08], p < 0.001). The number of patients who completed the 52-week trial without modifying their dose of OAD or insulin was low: 26 patients in the saxagliptin group, and 24 patients in the placebo group[2].

3.1.1 Comparative safety

Comparative safety data was limited to placebo-based comparisons as the company was unable to provide comparator information (see Sections 2.2 and 3.2). During the 12-week study period, patients were treated with saxagliptin for a mean duration of 74.5 ± 23.9 days (range: 2–120 days), while patients receiving placebo were treated for 80.3 ± 16.3 days (range: 15–124 days)[12]. The reported safety profile in the total population is in line with the findings from previous saxagliptin trials[16–19]; however, in patients with moderate and severe renal impairment, the incidence of adverse events (AE) was greater in the saxagliptin group compared to placebo (moderate: 41.7% vs. 33.3%, severe: 61.1% vs. 52.2%)[12]. Interestingly, within each treatment group, the incidence of serious AEs was greater in patients with moderate renal impairment compared to those with severe renal impairment (saxagliptin: 14.6% vs. 11.1%, respectively; placebo: 11.9% vs. 4.3%, respectively)[5], which suggests that the AE profile is more dependent on the underlying disease (TD2M) rather than the degree of renal dysfunction.

The types of AEs reported in the 52-week phase were similar to those reported in the 12-week phase[5], although the incidence of serious AEs increased in the 52-week period compared to the 12-week period in patients receiving saxagliptin (27.1% vs. 14.1%) and in patients receiving placebo (28.2% vs. 8.2%). These figures, however, are not unexpected given the severity of renal disease in the study population[5].

3.2 WMP critique

- In light of the lack of comparator information, the company's submission was limited to placebo-controlled data only[2].
- The company submission proposes the use of saxagliptin 2.5 mg in T2DM patients with moderate and severe renal failure[2]. The original indication supports the use of saxagliptin in T2DM patients after metformin, a sulphonylurea or a thiazolidinedione[1]. Metformin is contraindicated in patients with moderate or severe renal impairment, however in the licence extension study no patients were receiving a thiazolidinedione, and only 20% of patients in the saxagliptin group were receiving a sulphonylurea[12].
- Caution is advised when interpreting the primary endpoint in terms of renal impairment as the baseline distribution of patients was biased towards moderate renal impairment (see Table 1); and the distribution of patients in each renal impairment category after the 12-week and 52-week treatment periods was not disclosed. The Committee for Medicinal Products for Human Use (CHMP) highlighted that the number of patients in the severe renal impairment group was low; the Summary of Product Characteristics (SPC) reflects that experience in this group is limited[1,5].
- The study assessing the efficacy of saxagliptin 2.5 mg versus placebo in patients with moderate and severe renal impairment met the primary efficacy endpoint (change in HbA1c at week 12) in favour of saxagliptin[12]. However, the company did not include in their submission any information regarding

sensitivity analyses to validate the primary findings[2]. Several supporting analyses are presented in the original study paper[12] and in the European Public Assessment Report for Onglyza®▼[5]: it was reported that the primary endpoint lost statistical significance when a more conservative imputation approach (BOCF) was used, although it reportedly did not have a large effect on the overall results[5].

- No reference was provided for the figures stated by the company relating to the potential use of saxagliptin in Wales.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

The limited submission provided by the company[2] does not include any evidence on the cost-effectiveness of saxagliptin 2.5 mg tablets for improving glycaemic control in adult patients aged 18 years and older with T2DM with moderate or severe renal impairment. Cost-effectiveness evidence is not required for a limited submission.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

According to the company's estimates, based on the prevalence of T2DM in Wales and UK prescription data (no further details provided), there are currently 245 T2DM patients with renal impairment in Wales who are eligible for saxagliptin treatment. This number is expected to increase to 432 patients in year two, 572 patients in year three, 719 patients in year four and 874 patients in year five (a basis for these estimates is not provided). The company estimates that the cost of treatment of these patients with saxagliptin would be £62,417 in year one, rising to £222,878 in year five (calculations are not provided). In comparison, the company estimates the cost of treatment with pioglitazone would be £105,418 in year one and £376,428 in year five, and exenatide treatment would cost £6,096,546 in year one and £21,769,509 in year five (calculations are not provided).

5.1.2 WMP Critique

There is a lack of transparency in the company's estimates of eligible patient numbers, and hence the budget implications of the use of saxagliptin in NHS Wales. The basis for assuming 245 patients will be eligible for treatment in year 1 is not clear, nor is there a breakdown of whether these patients have moderate or severe renal impairment (for which the SPC notes experience with saxagliptin is very limited[1]). A basis for the anticipated increase in eligible patient numbers in subsequent years is not provided, and it is not clear if these estimates account for any potential discontinuation of saxagliptin, for example, due to progression to end stage renal failure (for which saxagliptin is not licensed).

It is unclear how the total annual costs of treatment with saxagliptin, pioglitazone and exenatide have been calculated. Given that acquisition costs for exenatide are approximately twice those of saxagliptin (see Table 2), it is unclear why the company has estimated comparative exenatide costs that are several orders of magnitude greater.

As it is not possible to verify the approaches taken and to determine the reliability of the company's estimates, the budget impact analysis is of limited informative value.

5.2 Comparative unit costs

Table 2 shows example annual drug acquisition costs for agents that may be used in the treatment of adult patients aged 18 years and older with T2DM with moderate to severe renal impairment. It should be noted that these agents would be used in combination with other agents, the costs of which are not included in Table 2.

Table 2. Example acquisition costs for saxagliptin, pioglitazone and exenatide in the treatment of adult patients aged 18 years and older with type 2 diabetes mellitus with renal impairment.

Drug	Regimen	Annual cost per patient (£)
Onglyza®▼ (saxagliptin) 2.5 mg tablets	2.5 mg once daily	411
Actos®▼ (pioglitazone) 15 mg, 30 mg and 40 mg tablets	15–30 mg once daily increased to 45 mg once daily according to response	336–514
Byetta®▼ (exenatide) 5 micrograms and 10 micrograms solution for injection pre-filled pen	5–10 microgram twice daily	830
Costs are based on MIMS[20] list prices. Table does not include the costs of other agents, which may be given in combination with the above. See relevant SPCs 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

WMP is of the opinion that saxagliptin is suitable for shared care within NHS Wales.

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