

saxagliptin 2.5mg and 5mg film-coated tablets (Onglyza[®])

SMC No. (918/13)

Bristol-Myers Squibb/AstraZeneca

08 November 2013

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

saxagliptin (Onglyza[®]) is accepted for restricted use within NHS Scotland.

Indication under review: 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.

SMC restriction: as an alternative dipeptidyl peptidase-4 inhibitor option.

Treatment with saxagliptin reduces glycosylated haemoglobin, HbA1c, levels significantly more than placebo when used in combination with metformin and a sulphonylurea. Indirect comparisons demonstrated similar efficacy to other dipeptidyl peptidase-4 inhibitors.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

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.

Dosing Information

5mg orally once daily

Product availability date

17 January 2013

Summary of evidence on comparative efficacy

Type 2 diabetes mellitus is a chronic progressive disease involving insulin resistance, impaired insulin secretion, and increased glucose production. Saxagliptin inhibits the enzyme dipeptidyl peptidase-4 (DPP-4) preventing the degradation of incretin hormones which are released from gut cells in response to a meal. These hormones stimulate insulin release and attenuate glucagon secretion in response to raised blood glucose levels. SMC has previously accepted saxagliptin for restricted use as add-on combination therapy with metformin, when metformin alone, with diet and exercise, does not provide adequate glycaemic control. This submission is for a further extension to the marketing authorisation for saxagliptin to include use as triple oral therapy in combination with metformin and a sulphonylurea.

The evidence to support this extension to the marketing authorisation comes from results of one multi-centre, randomised, double-blind phase IIIb study.^{1,2} The study enrolled patients aged ≥ 18 years, with type 2 diabetes with inadequate glycaemic control (defined as glycosylated haemoglobin, HbA1c, $\geq 7\%$ and $\leq 10\%$) despite treatment with metformin and a sulphonylurea for ≥ 8 weeks. Inclusion criteria specified that the metformin dose was to be the maximum tolerated dose with a minimum of $\geq 1,500\text{mg}$ daily and the sulphonylurea dose to be at maximum tolerated dose being $\geq 50\%$ of the maximum recommended dose. Eligible patients were randomised in a ratio of 1:1 to receive saxagliptin 5mg (n=129) or matching placebo (n=128) orally once daily for 24 weeks. During the 24-week double-blind treatment period, doses of concomitant metformin and sulphonylurea remained stable.

The primary outcome was the change from baseline to week 24 in HbA1c in the full analysis set (all randomised patients who received at least one dose of study drug and had a baseline and at least one post-baseline value in at least one efficacy parameter). An analysis of co-variance was used, with treatment and country as fixed effects, and baseline HbA1c as a co-variate. Missing data at 24 weeks were imputed using last observation carried forward. The primary outcome and the three secondary outcomes were tested in a fixed sequence to control the Type I error rate so as not to exceed the 5% level.¹

At baseline, the mean HbA1c was 8.37% (standard error [SE] 0.08%) in the saxagliptin group and 8.17% (SE 0.07%) in the placebo group. At week 24, the mean adjusted change was -0.74% (SE 0.08%) in the saxagliptin group and -0.08% (SE 0.07%) in the placebo group. The

difference in adjusted mean change significantly favoured saxagliptin with a difference of -0.66% (95% confidence interval [CI]: -0.86% to -0.47%, $p < 0.0001$).¹

Secondary outcomes included changes from baseline to 24 weeks in post-prandial glucose (PPG, measured 2 hours after breakfast) and in fasting plasma glucose (FPG). At week 24, the mean adjusted change in PPG was -11.66 (SE 5.95) mg/dL in the saxagliptin group and +5.08 (SE 5.85) mg/dL in the placebo group, corresponding to a significant difference of -16.74 mg/dL (95% CI: -31.85 to -1.62, $p = 0.03$). At week 24, the mean adjusted change in FPG was -5.28 (SE 3.75) mg/dL in the saxagliptin group, and +2.62 (SE 3.60) mg/dL in the placebo group, corresponding to a numerical, but not significant, difference of -7.90 mg/dL (95% CI: -16.96 to 1.15, $p = 0.087$). The third secondary outcome was the proportion of patients achieving a glycaemic response of HbA1c $< 7.0\%$ and was achieved in 31% (39/127) of saxagliptin and 9.4% (12/128) of placebo patients at week 24. However, under the fixed sequence testing, since the treatment difference for change in FPG was not significant, statistical significance testing of the comparison of HbA1c responder rates was not considered appropriate.¹

There were no clinically relevant effects with saxagliptin compared with placebo on mean changes from baseline to week 24 in fasting plasma lipids, fasting levels of insulin, C-peptide and glucagon.¹

Quality of life was assessed during the study using the EuroQol-5 dimension questionnaire (EQ-5D) and the changes from baseline to week 24 were similar in the saxagliptin and placebo groups.¹

Summary of evidence on comparative safety

During the pivotal study, adverse events were reported by 63% (81/129) saxagliptin and 72% (91/128) placebo-treated patients and were considered to be treatment-related in 16% (21/129) and 10% (13/128) of patients respectively. Serious adverse events were reported in 2.3% (3/129) saxagliptin and 5.5% (7/128) placebo treated patients. In the saxagliptin group, 0.8% (1/129) of patients discontinued due to adverse events compared to 2.3% (3/128) of placebo patients.¹

In the saxagliptin group, 10% (13/129) of patients experienced 19 hypoglycaemic adverse events compared with 6.3% (8/128) of placebo patients experiencing 16 hypoglycaemic adverse events. There were no serious hypoglycaemic adverse events. Two saxagliptin treated patients had confirmed hypoglycaemic adverse events (by fingerstick glucose value of ≤ 50 mg/dL). During the double-blind treatment period, the sulphonylurea dose was reduced in one saxagliptin and two placebo patients because of hypoglycaemic events.¹

The safety profile of saxagliptin was similar to that of placebo and there were no unexpected adverse events. The most frequently reported adverse events in the saxagliptin group were nasopharyngitis (6.2%), diarrhoea (5.4%) and hypertension (5.4%), and in the placebo group were nasopharyngitis (9.4%), urinary tract infection (6.3%) and dyslipidaemia (5.5%).¹

Summary of clinical effectiveness issues

Saxagliptin has been accepted by SMC for restricted use in combination with metformin when diet and exercise plus metformin do not provide adequate glycaemic control. This extension to the marketing authorisation is for use as triple oral therapy with metformin and a sulphonylurea. Saxagliptin is one of four DPP-4 inhibitors licensed for use as triple oral therapy with metformin and a sulphonylurea in patients with type 2 diabetes. Linagliptin, sitagliptin and vildagliptin have been accepted for use in this indication by SMC. Clinical experts consulted by SMC have advised that sitagliptin is the predominant DPP-4 inhibitor prescribed in Scotland and this is supported by Scottish prescribing data.

The pivotal studies demonstrated that treatment with saxagliptin reduces HbA1c levels significantly more than placebo when used in combination with metformin and a sulphonylurea. Although reduction in HbA1c levels is an accepted surrogate endpoint commonly used in diabetes studies, evidence of benefit for longer term clinical endpoints such as reduced microvascular or macrovascular outcomes is lacking. Treatment guidelines recommend HbA1c targets in the treatment of diabetes. The way in which HbA1c results are expressed in the UK has changed recently; results are now reported as mmol/mol rather than as a percentage. The equivalent of the HbA1c targets of 6.5% and 7.0% are 48mmol/mol and 53mmol/mol in the new units.

There is no direct comparative study evidence for saxagliptin versus a relevant active comparator when used as triple oral therapy in combination with metformin and a sulphonylurea. Therefore, the submitting company performed two adjusted indirect comparisons using the simple Bucher method to compare saxagliptin with sitagliptin and saxagliptin with linagliptin using placebo as the common comparator. The comparisons included three studies: one for each active agent versus placebo when used as part of triple oral therapy with metformin and a sulphonylurea for patients with type 2 diabetes who have inadequate glycaemic control on metformin and sulphonylurea alone.^{1,3,4} Only a subgroup of the sitagliptin study population was used in the comparison but this study was designed to have at least 90% power to detect a 0.5% difference between sitagliptin and placebo for each subgroup. There were some differences between patients enrolled in each of the studies, particularly between the saxagliptin and sitagliptin studies which included a proportion of patients who were treatment-naïve at enrollment as well as patients taking various other combinations. There were also possible differences in rescue medication between studies and in the sitagliptin study, glimepiride was the only sulphonylurea used which does not reflect Scottish practice. Results of the indirect comparisons suggested that there were no significant differences between saxagliptin and both sitagliptin and linagliptin in terms of reducing HbA1c. The comparison of safety outcomes may be less robust as there may be more subjectiveness in their reporting. Since the economic case is based on cost-minimisation, it was assumed that the treatments are equivalent in terms of safety.

Summary of comparative health economic evidence

The company submitted a simple cost-minimisation analysis comparing saxagliptin with sitagliptin and linagliptin as an alternative DPP-4 inhibitor in adults 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. The submitting company justified the comparators on the basis that both

treatments have been accepted by SMC for restricted use in the indication being considered for saxagliptin. The base case analysis used a one year time horizon with a five year time horizon explored in the sensitivity analysis.

The data to support comparable efficacy were based on indirect comparison of saxagliptin with sitagliptin and linagliptin. The company conducted two adjusted indirect comparisons using the Bucher method to compare saxagliptin with sitagliptin and linagliptin using placebo as the common comparator. The indirect comparisons suggested that there were no significant differences between saxagliptin and both sitagliptin and linagliptin in terms of reducing HbA1c. This supports the assumption of comparable efficacy which underpins the cost-minimisation analysis.

Only the drug acquisition costs of saxagliptin, linagliptin and sitagliptin were included. Compliance was also considered to be equivalent between the therapies. Other costs, such as renal and liver monitoring costs, were excluded on the basis that these costs would apply equally to both arms as all treatments would be taken in combination with metformin and a sulphonylurea and would therefore require a similar level of monitoring.

Over a one year time horizon, the cost of saxagliptin was estimated to be £410.80 per patient compared with £432.38 for both sitagliptin and linagliptin. The cost-minimisation analysis showed that saxagliptin would be cost-saving compared with both sitagliptin and linagliptin with savings of £21.58 per patient. When the time horizon was increased to five years, saxagliptin remained cost-saving with the savings increasing to £97.43 by year 5.

Despite the lack of direct comparative data, the indirect comparisons indicate comparable efficacy between saxagliptin and both linagliptin and sitagliptin. While the Bucher method is not considered the most robust method when conducting indirect comparisons, it is reasonable to conclude there are no significant differences between the treatments. As saxagliptin has a lower drug acquisition cost and requires the same level of monitoring as sitagliptin and linagliptin, saxagliptin is the preferred treatment on cost-minimisation grounds. Therefore, the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guideline Network (SIGN) published guideline 116, Management of diabetes: A National Clinical Guideline in March 2010.⁵ It states that DPP-4 inhibitors may be used to improve blood glucose control in people with type 2 diabetes but notes that published studies for sitagliptin and vildagliptin have medium term follow up (maximum of two years) therefore the long term effects of these drugs on microvascular complications, cardiovascular disease and mortality are unknown.

The National Institute for Health and Care Excellence (NICE) published clinical guideline 87: Type 2 diabetes: the management of type 2 diabetes in May 2009.⁶ It recommends considering the addition of a DPP-4 inhibitor as second- or third-line therapy in specific circumstances. This guideline predates the availability of saxagliptin.

The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) published a position statement “Management of Hyperglycaemia in type 2 diabetes: a patient-centred approach” in June 2012.⁷ This suggests a number of treatment options for triple therapy with no specific preference: choice is based on patient and drug characteristics.

Additional information: comparators

The other DPP-4 inhibitors (linagliptin, sitagliptin and vildagliptin) are licensed for use as triple oral therapy in combination with metformin and a sulphonylurea when this regimen alone with diet and exercise does not provide adequate glycaemic control.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Saxagliptin	5mg orally once daily	411
Linagliptin	5mg orally once daily	432
Sitagliptin	100mg orally once daily	432
Vildagliptin	50mg orally twice daily	413

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 21 August 2013.

Additional information: budget impact

The gross impact on the medicines budget was estimated to be £29k in year 1 and £338k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is assumed to be savings of £2k and £18k in years 1 and 5 respectively.

The submitting company estimated the population eligible for treatment to be 784 in year 1 rising to 3,920 in year 5.

The company explored two scenario analyses as follows:

- Assuming patients remain on a DPP-4 inhibitor for 3 years. The gross impact on the medicines budget was estimated to be £29k in year 1 and £203k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is estimated to result in savings of £2k and £11k in years 1 and 5 respectively.
- Assuming patients remain on a DPP-4 inhibitor for 1 year. The gross impact on the medicines budget was estimated to be £29k in year 1 and £68k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is estimated to result in savings of £2k and £4k in years 1 and 5 respectively.

Other data were also assessed but remain commercially confidential.*

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. European Medicines Agency, European Public Assessment Report for saxagliptin (Onglyza®) EMEA/H/C/1039/WS/0295 17 January 2013 www.ema.europa.eu [accessed 31 July 2013]
2. www.clinicaltrials.gov [ClinicalTrials.gov Identifier NCT01128153]
3. Hermansen K, Kipnes M, Luo E, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. *Diabetes Obes Metab* 2007;9:733-45.
4. Owens DR, Swallow R, Dugi KA, et al. Efficacy and safety of linagliptin in persons with type 2 diabetes inadequately controlled by a combination of metformin and sulphonylurea: a 24-week randomized study. *Diabet Med* 2011;28:1352-61.
5. Scottish Intercollegiate Guidelines Network (SIGN). Management of Diabetes: A national clinical guideline. Publication No 116, March 2010;
6. National Institute for Health and Care Excellence, Type 2 Diabetes: Management of Type 2 Diabetes (Clinical Guideline 87), 2009.
7. Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycaemia in type 2 diabetes: a patient-centred approach. *Diabetes Care* 2012;35:1364-79.

This assessment is based on data submitted by the applicant company up to and including 10 September 2013.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.