Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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# saxagliptin, 2.5mg and 5mg, film-coated tablets (Onglyza®) SMC No. (772/12)

## Bristol-Myers Squibb/AstraZeneca

10 October 2014

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 NHS Scotland. The advice is summarised as follows:

**ADVICE**: following a full submission

**saxagliptin (Onglyza®)** is accepted for 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 combination therapy with insulin (with or without metformin), when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.

A phase IIIb, randomised, double-blind, placebo-controlled, parallel-group study in adult patients with type 2 diabetes mellitus and inadequate glycaemic control on a stable dose of insulin showed that addition of saxagliptin 5mg daily was superior to placebo for the primary endpoint of change from baseline in HbA1c at 24 weeks.

The manufacturer's submission related only to the use of saxagliptin in combination with insulin (with or without metformin). SMC cannot recommend the use of saxagliptin as monotherapy.

Overleaf is the detailed advice on this product.

**Chairman,**
**Scottish Medicines Consortium**

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## Indication

In adult patients aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control . as combination therapy with insulin (with or without metformin), when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.

## Dosing Information

The recommended dose of saxagliptin is 5mg once daily. Saxagliptin can be taken with or without a meal at any time of the day.
The dose of saxagliptin should be reduced to 2.5mg in patients with moderate to severe renal impairment.

## Product availability date

November 2011

## 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 the gut cells in response to a meal.[1] 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; and 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. This submission is for a further extension to the marketing authorisation to the use of saxagliptin in combination with insulin (with or without metformin), when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.

The clinical evidence derives from one phase IIIb, randomised, double-blind, placebo-controlled, parallel-group study (study 057) in patients with type 2 diabetes mellitus.[2] Patients were eligible if they were aged 18 to 78 years with a fasting C-peptide ≥0.8ng/mL, body mass index (BMI) ≤45kg/m$^2$ and inadequate glycaemic control (HbA1c 7.5% to 11.0%) on a stable dose of insulin (30 to 150units/day with ≤20% variation in total daily dose for ≥8 weeks before screening). Patients could also be taking metformin if the daily dose was stable for ≥8 weeks before screening, with a maximum of 75% of patients taking metformin at baseline permitted. No other antidiabetic medications were permitted. Patients were eligible for randomisation if, during the a 4-week, single-blind dietary and exercise run-in period, HbA1c remained ≥7.5% and ≤11%; compliance was ≥80% for use of study medication and for recording glucose values and insulin doses, and the mean total daily insulin dose was within 20% of the mean total daily dose at screening. Patients were advised to keep insulin therapy as stable as possible; however, insulin could be down-titrated at the discretion of the investigator. Patients were randomised in a 2:1 ratio to receive saxagliptin 5mg (n=304) or placebo (n=151) orally once daily with stratification for metformin use. Treatment was continued for 24 weeks, after which patients could continue onto an extension double-blind phase up to 52 weeks.

The primary outcome was change in HbA1c from baseline to week 24, evaluated in all patients who received at least one dose of study medication and had a baseline and at least one post-baseline measurement. Baseline HbA1c was 8.7% for saxagliptin and 8.6% for placebo. After 24 weeks, the adjusted mean change in HbA1c was -0.73% for saxagliptin 5mg versus -0.32% for placebo; a significant difference of -0.41% (95% confidence interval [CI]: -0.59 to -0.24)[2], and this was maintained at 52 weeks (treatment difference of -0.37% [95% CI: -0.55 to -0.19]).[3]

In a randomised, double-blind, placebo-controlled study in 170 patients with type 2 diabetes mellitus and moderate or severe renal impairment or end-stage renal disease, saxagliptin 2.5mg was superior to placebo for the primary outcome of absolute change from baseline to week 12 in HbA1c (treatment difference of -0.42% [95% CI: -0.71 to -0.12%]), and this was maintained to week 52 (treatment difference of -0.73% [95%CI: -1.11% to -0.34%]). The majority of patients were receiving insulin therapy at baseline (84% in the saxagliptin group and 67% in the placebo group).[4,5]

## Summary of evidence on comparative safety

In study 057, 66% (202/304) of patients in the saxagliptin group and 72% (108/151) in the placebo group experienced an adverse event, of which 18% (56/304) and 23% (34/151) were considered treatment-related. At least one serious adverse event occurred in 8.2% (25/304) of patients in the saxagliptin group and 8.6% (13/151) in the placebo group. The safety profile of saxagliptin was similar to placebo and there were no unexpected adverse events.

Infections were reported in both treatment groups and included urinary tract infection (7.9% in both groups), nasopharyngitis (6.3% saxagliptin versus 6.6% placebo), upper respiratory tract infection (6.3% versus 7.3%), pharyngitis (3.6% versus 5.3%), and influenza (3.3% versus 9.3%).[3]

Hypoglycaemia was reported in 23% of patients in the saxagliptin group and 27% in the placebo group, and confirmed hypoglycaemia (fingerstick glucose ≤50mg/dL) occurred in 7.6% versus 6.6% of patients respectively.[3]

## Summary of clinical effectiveness issues

This submission relates to an extension to the marketing authorisation for saxagliptin for use in combination with insulin (with or without metformin). Saxagliptin is one of five DPP-4 inhibitors licensed for use in combination with insulin; however, none has been accepted for use within NHS Scotland in this setting. The glucagon-like peptide-1 (GLP-1) receptor agonists exenatide and lixisenatide, the thiazolidindione pioglitazone and the sodium glucose co-transporter 2 (SGLT2) inhibitors canagliflozin and dapagliflozin have been accepted for use within NHS Scotland in combination with insulin. If accepted by SMC, saxagliptin would offer another treatment option for add-on to insulin in this patient population.

Study 057 demonstrated that treatment with saxagliptin 5mg reduces HbA1c significantly more than placebo when used in combination with insulin (±metformin) up to 52 weeks. The treatment effect was modest, however it was considered clinically relevant by the European Medicines Agency.[6] A supportive study showed that saxagliptin 2.5mg was superior to placebo in reducing HbA1c in patients with moderate to severe renal impairment. Although reduction in HbA1c levels is an accepted surrogate endpoint commonly used in diabetes studies, there is no evidence of benefit for longer term clinical endpoints such as reduced microvascular or macrovascular complications. A large phase IV randomised, placebo-controlled study showed no difference in cardiovascular outcomes between saxagliptin and placebo.[7]

There are no direct comparative studies with other medicines used in combination with insulin in this patient population. To support the economic case, the company presented a Bayesian network meta-analysis (NMA) and several Bucher indirect comparisons of saxagliptin versus the relevant comparators (exenatide and lixisenatide). The analyses included seven studies of adults with type 2 diabetes with inadequate glycaemic control despite treatment with an insulin-containing regimen. Several outcomes were compared: mean change from baseline in HbA1c, weight and systolic BP, and the proportion of patients experiencing at least one hypoglycaemic episode. The base-case fixed-effects Bayesian NMA suggested that saxagliptin, exenatide and lixisenatide were associated with similar changes in HbA1c. However, saxagliptin was likely to lead to weight gain (estimated difference of 1.5 to 3kg) when compared with the GLP-1 agonists. The results showed similar risk of hypoglycaemia for saxagliptin, exenatide and lixisenatide; however, due to differences in the definition of hypoglycaemia in the included studies, the comparison for this outcome is of uncertain validity.

Saxagliptin is administered orally, which may be considered an advantage over comparator treatments that are administered by subcutaneous injection. However, no data was provided in the submission on quality of life or patient preferences.

## Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing saxagliptin with the GLP-1 agonists exenatide (twice daily) and lixisenatide. The submitting company presented its analysis for the saxagliptin use in combination therapy with insulin (with or without metformin), when this regimen alone, with diet and exercise, does not provide adequate glycaemic control. There is some uncertainty over the appropriateness of the comparators in the submission as SMC clinical experts indicated sitagliptin may be the treatment most likely to be displaced by saxagliptin. Sitagliptin was not included as a comparator by the submitting company as it has been not recommended for use by SMC in this setting due to company non-submission. GLP-1 agonists and dapagliflozin were also mentioned by the experts as possible treatments that could be displaced by saxagliptin.

A Discrete Events Simulation model is used in the analysis, with a 40 year time horizon. The model is similar to previous diabetes models submitted to SMC as short-term surrogate outcomes are modelled to determine long-term outcomes using United Kingdom Progressive Diabetes study (UKPDS) data. Patients enter the simulation model and at this point baseline characteristics, such as BMI, HbA1c, systolic blood pressure (SBP) and modifiable risk factors for long-run micro- and macrovascular complications, are assigned to the patient. Microvascular complications include blindness, amputation and nephropathy. Macrovascular complications include ischemic heart disease, myocardial infarction, congestive heart failure and stroke. The model simulates efficacy, adverse events, discontinuation, costs, utilities and weight changes. At the end of each six-month cycle, risk equations from the UKPDS data estimate the occurrence of the complications as well as all-cause diabetes death. Patients progress through the model with the patients' risk factor continually being updated as each six monthly cycle passes until death or the end of the time horizon. A limitation of diabetes models is that they use surrogate outcomes, for example to determine long-term macro and microvascular complications, which may introduce some uncertainty. However, surrogate outcomes are often used in these models and have been accepted by SMC previously.

The clinical evidence used to support the analysis is from the results of the NMA described above which examined various outcome measures including HbA1c, weight and hypoglycaemia. The Bucher indirect comparison, also described above, was used to derive evidence for SBP in the economic model for the comparison with saxagliptin and exenatide twice daily but no data for SBP were available for the comparison with lixisenatide and thus a value of zero was assumed.

Utility decrements associated with complications, hypoglycaemia, weight changes, urinary tract infection and other adverse events were included in the analysis. These were taken from a range of published literature. The sources of the utility values have been used in previous SMC submissions, including the utility value applied to changes in weight which was used in the dapagliflozin for triple therapy submission.

Costs included in the analysis were: drug acquisition costs, adverse events costs, costs associated with complications, hypoglycaemia costs, treatment discontinuation costs and costs associated with weight gain.

In the base case analysis for the comparison with exenatide twice-daily, the submitting company estimated saxagliptin would result in savings of £1,402 but would also be less effective (QALY–loss of 0.012) compared with exenatide twice daily. In the base case results for the comparison with lixisenatide, the submitting company estimated saxagliptin is dominant i.e. less expensive and more effective based on savings of £472 and a QALY gain of 0.010.

A range of sensitivity analysis was provided. For the comparison with exenatide twice daily, the results are most sensitive to using an alternative utility source for weight change where the QALY loss increased to 0.026. For the comparison of saxagliptin verses lixisenatide, in all scenarios saxagliptin is dominant over lixisenatide. It should be noted that these results include non-significant differences in HbA1c and hypoglycaemia.

The following weaknesses were highlighted:

- SMC clinical experts' responses suggested there is some uncertainty over the appropriateness of the comparators in the submission as sitagliptin may be the treatment most likely to be displaced by saxagliptin in practice. However, GLP-1 agonists and dapagliflozin were also mentioned by the experts as possible comparators and, as a result, the comparators were considered to be reasonable.

- When non-significant differences in outcomes from the NMA and indirect comparison were removed, the results indicated there would be savings of £1,402 with saxagliptin and a QALY loss of 0.006. For the comparison with lixisenatide, saxagliptin was estimated to result in savings of £992 and a QALY loss of 0.001. The small QALY loss in both analyses is due to saxagliptin being more likely to result in weight gain.

- The NMA could not account for heterogeneity, which may introduce some bias into the results.

In conclusion, while there was some uncertainty over the comparators, on balance, they were considered to be reasonable and thus 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 Guidelines Network (SIGN) published updated guidance on the "Management of diabetes" in March 2010.[2] The guideline recommends that treatment targets should be individualised to balance the harms of hypoglycaemia and weight gain with the benefits in reducing the risk of microvascular and macrovascular disease. Target glycosylated haemoglobin (HbA1c) of 7.0% (53mmol/mol) is reasonable in people with type 2 diabetes mellitus, and in newly diagnosed patients, this target may be intensified to 6.5% (48mmol/mol). The treatment algorithm notes several options for second and third-line treatment of type 2 diabetes mellitus to be added in combination with metformin and/or sulfonylurea; additional oral anti-diabetic drugs, pioglitazone or DPP-4 inhibitors; or injections of GLP-1 analogues or commencement of insulin. Treatment should be continued if an individualised target is reached or the HbA1c falls at least 0.5% in 3 to 6 months. With respect to using insulin in patients with type 2 diabetes, oral sulphonylurea and metformin therapy should be continued when insulin is initiated to maintain or improve glycaemic control. Once daily, neutral protamine Hagedorn insulin is the first choice of insulin to be used, but basal insulin analogues can be considered if there are concerns regarding the risk of hypoglycaemia. The bedtime basal insulin should be titrated against the morning or fasting glucose and if HbA1c targets are not reached then the addition of prandial insulin should be considered.

The National Institute for Health and Care Excellence (NICE) published NICE Clinical Guideline 87 – Type 2 diabetes - newer agents, in May 2009.[3] The guideline considered sulfonylurea, DPP-4 inhibitors or pioglitazone as suitable second-line options to be used in combination with metformin and advised on cost effective use of exenatide as a third-line agent. The guideline recommended that patients using basal insulin regimens (e.g. neutral protamine Hagedorn or long-acting analogues) be monitored for the need to increase the dose and/or intensify the regimen using short-acting insulin before meals, or pre-mixed insulin. Patients using pre-mixed insulin should be monitored to determine if they need further injections of short-acting insulin before meals or conversion to a basal-bolus regimen. Combination of pioglitazone and insulin was considered appropriate for patients; who have inadequate glycaemic control despite high-dose insulin therapy; or who have had a significant response to thiazolidinedione therapy in the past.

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.[4] A patient-centred approach is advocated with individualisation of treatment. Beyond lifestyle advice and initial drug therapy with metformin a number of treatment options are recommended with no specific preference: choice is based on patient and drug characteristics.

## Additional information: comparators

Exenatide, lixisenatide, pioglitazone, canagliflozin*, dapagliflozin*

* Canagliflozin and dapagliflozin were recently accepted by SMC in combination with insulin, so were not considered comparators in the company's submission.

None of the DPP-4 inhibitors have been accepted for use within NHS Scotland in combination with insulin.

## Cost of relevant comparators

| Drug | Dose Regimen | Cost per year (£) |
|---|---|---|
| **Saxagliptin** | **5mg orally once daily** | **411** |
| Exenatide | 5 to 10micrograms twice daily by subcutaneous injection | 828 |
| Lixisenatide | Maintenance dose of 20 micrograms once daily by subcutaneous injection | 657 |
| Canagliflozin | 100mg to 300mg orally once daily | 476 to 657 |
| Dapagliflozin | 10mg orally once daily | 476 |
| Sitagliptin‡ | 100mg orally once daily | 432 |
| Linagliptin‡ | 5mg orally once daily | 432 |
| Vildagliptin‡ | 50mg orally twice daily | 413 |
| Alogliptin‡ | 25mg orally once daily | 346 |
| Pioglitazone | 15 to 45mg orally once daily | 17 to 23 |

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 07/08/14.
‡Not accepted by SMC for use within NHS Scotland in combination with insulin.

## Additional information: budget impact

The submitting company estimated the gross medicines budget impact to be £572k in year 1 and £1.6m in year 5. As other medicines were assumed to be displaced, the net medicines budget was estimated to be a saving of £575k in year 1 and £1.3m in year 5. These estimates were calculated on the basis of confidential estimates of patient numbers and treatment uptake.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission.


1. Bristol Myers Squibb-AstraZeneca EEIG, Saxagliptin (Onglyza®) Summary of product characteristics, last updated 26 June 2014. www.medicines.org.uk

2. Barnett AH, Charbonnel B, Donovan M et al. Effect of saxagliptin as add-on therapy in patients with poorly controlled type 2 diabetes on insulin alone or insulin combined with metformin. Current Medical Research & Opinion 2012; 28 (4): 513 to 523.

3. Barnett AH, Charbonnel B, Li J, Donovan M et al. Saxagliptin add-on therapy to insulin with or without metformin for type 2 diabetes mellitus: 52-week safety and efficacy. Clin. Drug Investig. (2013); 33: 707 to 717.

4. Nowick M, Rychlik H, Haller H et al. Saxagliptin improves glycaemic control and is well tolerated in patients with type 2 diabetes mellitus and renal impairment. Diabetes, Obesity and Metabolism 2011; 13: 523-532.

5. Nowick M, Rychlik H, Haller H et al. Long-term treatment with the dipeptidyl peptidase-4 inhibitor saxagliptin in patients with type 2 diabetes mellitus and renal impairment: a randomized controlled 52-week efficacy and safety study. Int. J. Clin. Pract. 2011; 12: 1230-39.

6. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP) assessment report EMA/43321/2012, Onglyza® saxagliptin, October 2011.

7. Scirica B, Bhatt DL, Braunwald E et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. New Engl. J. Med. 2013; 369: 1317-26.


This assessment is based on data submitted by the applicant company up to and including 11 August 2014.

**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.*