Scottish Medicines Consortium

saxagliptin, 5mg film-coated tablet (Onglyza®) No. (603/10)
Bristol-Myers Squibb Pharmaceuticals Ltd

05 February 2010

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 restricted use within NHS Scotland in adult patients with type 2 diabetes mellitus as add-on combination therapy with metformin, when metformin alone, with diet and exercise, does not provide adequate glycaemic control.

It is restricted to use in patients only when the addition of sulphonylureas is not appropriate, and represents an alternative to other agents such as thiazolidinediones.

Efficacy, as assessed by measurement of HbA1c, is comparable to another dipeptidyl peptidase-4 inhibitor. It appears to have minimal effect on body weight.

Saxagliptin is also licensed for use in combination with sulphonylureas or thiazolidinedione drugs for the treatment of type 2 diabetes. The manufacturer's submission related only to the use of saxagliptin in combination with metformin. SMC cannot recommend the use of saxagliptin in combination with sulphonylureas or thiazolidinediones.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

As add-on combination therapy, saxagliptin is indicated in adult patients 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.

It is also indicated
• 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.

The company did not provide data on saxagliptin use in combination with sulphonylureas or thiazolidinediones in the current submission therefore SMC has not considered these parts of the indication.

Dosing information

5mg once daily as add-on combination therapy with metformin

Product availability date

16 October 2009

Summary of evidence on comparative efficacy

Saxagliptin inhibits dipeptidyl peptidase 4 (DPP-4), the enzyme responsible for the inactivation of the incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Since these hormones stimulate insulin release, the DPP-4 inhibitor should result in a more sustained effect on glucose control.

For the part of the indication under review, the submitting company has requested that the Scottish Medicines Consortium considers the use of this product in a sub-set of the licensed indication; namely as add-on to metformin in patients who are failing to obtain sufficient glycaemic control on metformin alone, and in whom sulphonylureas are not appropriate.

The evidence supporting this submission comes from two randomised, double-blind studies: a placebo-controlled study of saxagliptin as add-on to metformin and an active controlled study of saxagliptin plus metformin versus sitagliptin plus metformin. Patients in both studies were adults with type 2 diabetes mellitus who were failing to obtain sufficient glycaemic control on metformin alone. Patients had been on their metformin dose, >1500mg daily, for at least 8 weeks, and had glycated haemoglobin (HbA1c) values between 7.0% (6.5% in the comparator study) and 10.0%, inclusive. In the placebo-controlled study there was an upper age limit of 77.

Both studies had a 2-week single-blind diet and exercise placebo lead-in period, when patients received open-label metformin at their pre-study dose: up to 2,500mg daily in the placebo-controlled study and 3,000mg in the comparator study. Patients were then randomised to receive treatment for 24 weeks in the placebo-controlled study and 18 weeks in the comparator study. In the placebo-controlled study, during the treatment phase, patients with inadequate glucose control were eligible for open-label pioglitazone as rescue

therapy and were counted as early discontinuers. Both rescued patients and those who completed the treatment period were eligible to enter a 42-month long-term extension phase, remaining on the initial treatment regime they had been randomised to. In both studies, the primary efficacy endpoint was the change in HbA1c from baseline to the end of the treatment period. Analysis was performed using an ANCOVA model with point estimates compared using a t-test. Secondary outcomes included change from baseline in mean fasting plasma glucose (FPG), proportion of patients achieving HbA1c < 7.0% (6.5% in the comparator study) and change in body weight.

In the placebo-controlled study, 743 patients were randomised equally to receive saxagliptin 2.5mg, 5mg or 10mg or placebo, daily, as add-on to their metformin treatment. Patients who were in the saxagliptin 2.5mg and 10mg groups will not be discussed further, as these doses are not included in the marketing authorisation. Analysis of the primary efficacy endpoint was in the randomised data set, with the last post-baseline measurement before week 24 or rescue being used if there was no week 24 measurement. Fifty-one percent of patients were male, mean age was 54.6 years and mean baseline HbA1c was 8.0%. The proportion of patients who discontinued the study due to lack of glycaemic control or need for glycaemic rescue was 27% in the placebo group and 13% in the saxagliptin 5mg group.

At week 24, treatment with saxagliptin 5mg daily as an add-on to metformin led to a mean reduction in HbA1c of 0.69% (from 8.07% to 7.37%), while placebo add-on resulted in an increase of 0.13%. This gave a statistically significant mean difference of -0.83% (95% confidence interval (CI): -1.02 to -0.63%). Reductions were observed from the first assessment point, at week 4, and reached a sustained maximum at week 12. A statistically significant difference in FPG of -1.28mmol/L for the saxagliptin 5mg group compared with placebo was observed. The proportion of patients achieving a therapeutic glycaemic response (HbA1c < 7.0%) on saxagliptin 5mg versus placebo was also statistically significant (44% versus 17%, a difference of 27% (95% CI: 17 to 37%). Combined therapy with saxagliptin 5mg and metformin did not affect mean body weight.

Results from the long-term extension are interim, but at 102 weeks show maintenance of the reduction in HbA1c seen with saxagliptin as add-on at 24 weeks.

The active-controlled 18-week study was designed to assess if the change from baseline in HbA1c achieved with saxagliptin 5mg daily added to metformin, was non-inferior to that achieved with sitagliptin 100mg daily added to metformin. Patients (n = 801) were randomised equally, with 677 in the per protocol set. Forty-eight percent were male, mean age was 58 years and mean baseline HbA1c was 7.7%. Analysis of the primary outcome was in the per protocol analysis set, using the last observation carried forward method and the non-inferiority margin was set at 0.3%.

Patients on saxagliptin plus metformin had a reduction in mean HbA1c of 0.52% (95% CI: -0.60 to -0.45%), from a baseline of 7.68%, compared to a mean HbA1c reduction of 0.62% (95% CI: -0.69 to -0.54%) for the sitagliptin plus metformin group from a baseline of 7.69%; a difference of -0.62% (95% CI: -0.69 to -0.54%). The mean difference between the saxagliptin and sitagliptin groups was 0.09% (95% CI: -0.01 to 0.20%), demonstrating non-inferiority. The mean change in FPG was -0.6mmol/L and -0.9mmol/L for the saxagliptin and sitagliptin groups, respectively, from mean baseline values of 8.86mmol/L and 8.89mmol/L; a difference of 0.30mmol/L. A similar proportion of patients in both groups achieved a therapeutic response (HbA1c ≤ 6.5%); 26% versus 29%. There were small mean decreases in body weight in both treatment groups: reductions of 0.41kg from a baseline of 85.64kg in the saxagliptin group and 0.44kg from a baseline of 85.52kg in the sitagliptin group with 95% CI: -0.7 to -0.2 for both groups.

Summary of evidence on comparative safety

In the placebo-controlled trial, 70% of the saxagliptin 5mg group and 65% of the placebo group experienced adverse events (AEs), with 18% in each group considered treatment-related. Serious AEs were reported for 4.2% and 2.8% of the patients in each group, although none were considered related to treatment. The addition of saxagliptin 5mg did not cause an increased risk of hypoglycaemia or weight gain and there was no discernible effect on lymphocyte count or other laboratory markers.

In the study comparing saxagliptin add-on to sitagliptin add-on, 47% patients in both groups experienced an AE, with 5.2% and 7.5% respectively being considered treatment-related. Treatment-related serious AEs occurred in 0.2% and 0.5% of patients respectively. The most common type of AE was infection (25% in each group). Hypoglycaemic AEs occurred in 3.2% of saxagliptin patients and 2.8% of sitagliptin patients. One patient in the sitagliptin group experienced a skin disorder and there were no cardiovascular AEs in the saxagliptin group, compared with two in the sitagliptin group. The numbers of patients with any marked laboratory abnormality were low and similar between groups.

Diabetes is associated with an elevated risk of cardiovascular disease and so a post-hoc pooled analysis of saxagliptin randomised controlled trials was performed for the US Food and Drug Administration. This showed no evidence of increased cardiovascular risk for patients exposed to saxagliptin.

Summary of clinical effectiveness issues

For the part of the indication under review, the submitting company has requested that the Scottish Medicines Consortium considers the use of this product in a sub-set of the licensed indication namely, as add-on to metformin in patients who are failing to obtain sufficient glycaemic control on metformin alone and in whom sulphonylureas are not appropriate. The pivotal studies did not specifically recruit patients in whom treatment with sulphonylureas was not appropriate.

The size of additional effect on HbA1c when saxagliptin is added to metformin is modest, although significant, and is similar to the effect of adding sitagliptin. Use of saxagliptin appears to have little effect on body weight.

Limitations of the clinical data include the following: cardiovascular endpoints have not been prospectively addressed in any saxagliptin studies; there are little data on patients over 75 years and long term efficacy and tolerability data are still at the interim analysis stage and thus of limited value. From a safety point of view, long term data are also needed on morbidity and mortality. A Cochrane review suggested that DPP-4 inhibitors may influence the immune system, and there is pre-clinical evidence to suggest that skin-related AEs are more common with saxagliptin treatment although no increased risk was observed in the clinical trial programme. These issues are being monitored within a risk management plan.

There are currently no data comparing saxagliptin in combination with metformin with vildagliptin or any thiazolidinediones, in combination with metformin.

Although rescue therapy is common in diabetes trials, the addition of other therapies presents challenges in the interpretation of results. Because determination of the need for rescue therapy is before the end of the active treatment phase, there will be a proportion of patients in the final analysis who will have data from their last pre-rescue therapy values

contributing to the overall efficacy analysis. Patients who are rescued early may carry forward different values from those who are rescued later. Increased rescue may result in larger estimates of effect and the last observation carried forward approach has been shown to produce biased estimates. In the placebo controlled study, 25% of patients in the placebo group and 12% in the saxagliptin arm required rescue therapy.

Summary of comparative health economic evidence

The manufacturer presented two comparisons:

- saxagliptin/metformin versus sitagliptin/metformin
- saxagliptin/metformin versus thiazolidinedione/metformin

where thiazolidinedione was a pooled analysis of treatment with rosiglitazone and pioglitazone. The comparators were appropriate. The patient population of interest was those requiring an add-on therapy to metformin alone and in whom sulphonylureas are inappropriate.

For the comparison of saxagliptin/metformin with sitagliptin/metformin the manufacturer asserted clinical equivalence based on the head-to-head trial. As a consequence, a comparison of the direct drug costs was presented. This resulted in an annual saving from use of saxagliptin/metformin of £22. The results therefore indicated that saxagliptin would be preferred on cost minimisation grounds.

For the comparison of saxagliptin/metformin with thiazolidinedione/metformin the CARDIFF type 2 diabetes model was used with a time horizon of 40 years. Clinical effects were drawn from a variety of sources:

- HbA1c changes of -0.657 for saxagliptin/metformin and -0.551 for thiazolidinedione/metformin were drawn from a mixed treatment comparison
- a weight change of -0.41 kg for saxagliptin/metformin was drawn from the more pessimistic of the two trials described previously
- a weight change of +1.50 kg for thiazolidinedione/metformin was taken from a rosiglitazone 8mg trial
- a relative risk of cardiovascular events of 1.72 for thiazolidinedione/metformin was drawn from a meta analysis of papers

This resulted in an additional 0.11 QALYs at an additional cost of £52 to yield a cost effectiveness estimate of £494 per QALY. The main source of the anticipated patient benefits was the direct impact of the anticipated weight changes. Sensitivity analysis indicated that the ICER increased to £6,402 if the weight changes were equalised between treatments. If no differences in the risk of cardiovascular events was assumed the cost per QALY was £909 or £23, 866 if gains were only in terms of changes in HbA1c.

There were some concerns with respect to the thiazolidinedione comparison such as

- weight effects being the overwhelming driver of the modelling results, with these being informally arrived at;
- largely relying upon rosiglitazone papers for weight changes and cardiovacular risks for thiazolidinediones, when the profile for pioglitazone appeared more favourable than that of rosiglitazone.

However, as noted above, sensitivity analysis provided reassurance that when changes were made to the assumptions on these parameters the cost-effectiveness ratios were still acceptable. As such, the economic case was demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was received from:

- Diabetes UK Scotland

Additional information: guidelines and protocols

SIGN guideline no. 55, Management of Diabetes, (published in November 2001) predates the use of drugs of this class, but is currently being updated.

NICE short clinical guideline 87, Type 2 diabetes: newer agents, (published in May 2009) is a partial update of clinical guideline 66 and discusses the use of DPP-4 inhibitors, although not saxagliptin in particular. It recommends considering adding a DPP-4 inhibitor (sitagliptin or vildagliptin) instead of a sulphonylurea as second-line therapy to first-line metformin when control of blood glucose remains or becomes inadequate. This would be if the patient is at significant risk of hypoglycaemia or its consequences, or if they do not tolerate a sulphonylurea or it is contraindicated. It also discusses situations where a DPP-4 inhibitor may be preferable to a thiazolidinedione.

Additional information: comparators

Many anti-diabetic drugs are licensed for use with metformin in the treatment of type 2 diabetes mellitus and their costs are compared below. These costs do not include the price of metformin.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
saxagliptin	**5mg daily, orally**	**411**
liraglutide	1.2mg to 1.8mg daily, subcutaneously	952 to 1,428
exenatide	5 to 10 micrograms twice daily, subcutaneously	828
rosiglitazone	4 to 8mg daily, orally	260 to 520
pioglitazone	15 to 45mg daily, orally	185 to 480
sitagliptin	100mg once daily, orally	432
vildagliptin	50mg twice daily, orally	413
repaglinide	maximum dose 16mg daily, orally	381
nateglinide	60 to 180mg three times daily, orally	295 to 336

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 1 December 2009.

Additional information: budget impact

The manufacturer estimated that 4,576 patients would be eligible for treatment, based on Scottish prevalence rates coupled with UK prescription data of the proportion of patients on dual therapy with either DPP-IV inhibitor/metformin or thiazolidinedione/metformin. The share of the market for add-on therapy with a thiazolidinedione or DPP-IV inhibitor was estimated at 5% (229 patients) in year 1, rising to 25% (1,277 patients) by year 5. On this basis the gross drug cost of saxagliptin was estimated at £99k in year 1, rising to £554k by year 5. Given cost offsets the net drug cost was estimated at £11k in year 1, rising to £63k by year 5.

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.

This assessment is based on data submitted by the applicant company up to and including 15 January 2010.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

DeFronzo RA, Hissa MN, Garber AJ et al. The Efficacy and Safety of Saxagliptin When Added to Metformin Therapy in Patients With Inadequately Controlled Type 2 Diabetes on Metformin Alone. Diabetes Care. 2009;32(9):1649-55.

DeFronzo R, Hissa MN, Garber AJ et al. Once-daily saxagliptin added to metformin provides sustained glycemic control and is well tolerated over 102 weeks in patients with type 2 diabetes. Poster to be presented at the American Diabetes Association Annual Meeting 2009.

European Medicines Agency. European Public Assessment Report: Onglyza®. October 2009. EMEA H-C-1039
www.emea.europa.eu