Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

linagliptin, 5mg film-coated tablet (Trajenta®) SMC No. (746/11)

Boehringer Ingelheim / Eli Lilly and Company Ltd

09 December 2011

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

linagliptin film-coated tablet (Trajenta®) is accepted for restricted use within NHS Scotland.

Indication under review: The treatment of type 2 diabetes mellitus to improve glycaemic control in adults:
As monotherapy
- in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to intolerance, or contra-indicated due to renal impairment

As combination therapy
- in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control
- in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control

SMC restriction: in combination therapy with metformin when diet and exercise plus metformin alone does not provide adequate glycaemic control in patients for whom the addition of a sulphonylurea is inappropriate.

In two randomised double-blind, controlled studies, linagliptin in combination with metformin was found to be non-inferior to a sulphonylurea plus metformin, and superior to placebo plus metformin in controlling glycaemia, measured by the change in glycosylated haemoglobin (HbA1c). Linagliptin was associated with similar rates of hypoglycaemia and changes in weight when compared with placebo. Linagliptin is one of a number of medicines in this class, some of which are available at a lower acquisition cost.

SMC cannot recommend the use of linagliptin as monotherapy or in combination with metformin and a sulphonylurea as the company's submission related only to its use in combination with metformin.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

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Dosing Information

The dose of linagliptin is 5mg once daily. When added to metformin treatment, the dose of metformin should be maintained, and linagliptin administered concomitantly.

Product availability date

19 September 2011

Summary of evidence on comparative efficacy

Linagliptin 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. [1] Linagliptin is indicated for use in type 2 diabetes as monotherapy or as combination therapy either with metformin or with a sulphonylurea plus metformin. The submitting company has requested that the Scottish Medicines Consortium (SMC) considers this product when positioned for use in combination therapy with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control in patients for whom the addition of a sulphonylurea is inappropriate.

Evidence for the indication under review is from two similarly designed randomised, double-blind, controlled, multi-centre phase III studies. One study used an active-control with a double-dummy design to maintain blinding, [2,3,6] and the second study was placebo-controlled. [4-6] Adults aged between 18 and 80 years with: type 2 diabetes; a body-mass index (BMI) ≤40kg/m^2; taking a stable dose of metformin (of at least 1,500mg per day or the maximum tolerated dose) and not more than one additional oral anti-diabetic medication were included in the studies. Prior to randomisation of treatment, patients' glycosylated haemoglobin (HbA1c) was to be between 6.5% and 10% in the active-controlled study or between 7% and 10% in the placebo-controlled study. Patients taking a second oral antidiabetic medicine in addition to metformin underwent a washout period in which metformin was continued at the same dosage and the second agent was discontinued. All patients underwent a two-week placebo run-in period prior to randomisation to either linagliptin 5mg daily, or control. Randomisation was stratified by HbA1c (<8.5% versus ≥8.5%) and the previous use of anti-diabetic medicines. [2-6]

In the active-controlled study, patients were allocated to glimepiride (1mg to 4mg daily) in a 1:1 ratio with linagliptin. [6] The primary endpoint was the change from baseline in HbA1c after 104 weeks of treatment and was tested on the Full Analysis Set (FAS), which comprised all randomised patients who had taken at least one dose of study medication, had a baseline and at least one on-treatment HbA1c measurement, and used last observation carried forward (LOCF) to impute missing data. [2,3,6] Approximately half of the patients in the glimepiride group were taking a dose of 4mg daily, with a mean dose of 3mg daily. [6] Treatment with linagliptin and metformin was associated with an adjusted mean change in HbA1c of -0.16% from a baseline of 7.69% after 104 weeks of treatment. The adjusted mean change in HbA1c associated with the glimepiride and metformin group was -0.36%. The difference between linagliptin and glimepiride in adjusted mean change of HbA1c from baseline to 104 weeks was 0.20% (97.5% confidence interval [CI]: 0.09 to 0.299), meeting the pre-specified non-inferiority margin of 0.35%. [1,3]

In the placebo-controlled study, patients were allocated in a 3:1 ratio to linagliptin or placebo respectively. Rescue medication permitted during the 24-week randomised period was the addition of sulphonylurea antidiabetic medicines. The primary outcome was the change in HbA1c from baseline to 24 weeks of treatment and linagliptin was found to be superior to placebo. After 24 weeks of treatment, linagliptin reduced HbA1c by 0.49% from a baseline of 8.09%. Patients assigned to placebo, with a mean baseline HbA1c of 8.02%, had a mean increase of 0.15% in HbA1c, resulting in a treatment difference of -0.64% (95% CI: -0.78 to -0.50). [4,5]

Relevant secondary endpoints in the studies included changes in bodyweight from baseline to the end of the study. Linagliptin was superior to glimepiride in the mean change in bodyweight from baseline to week 104 with a treatment difference of -2.9kg. [2] There was no significant difference between the treatment groups in the mean change in bodyweight from baseline to week 24 when linagliptin was compared with placebo (-0.4kg versus -0.5kg respectively). Rescue medication was required in significantly less patients in the linagliptin group compared with the placebo group (8% versus 19% respectively). [4] Of the patients in the placebo-controlled study who had a baseline HbA1c ≥7.0%, treatment with linagliptin was associated with a significantly higher probability of achieving a target HbA1c <7.0% at 24 weeks compared with placebo (26% versus 9%): an odds ratio of 4.4 (95% CI: 2.4 to 8.0). [4]

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

Summary of evidence on comparative safety

Fewer patients treated with linagliptin experienced adverse events compared with glimepiride (85% versus 91% respectively). Treatment-related adverse events were reported in 15% of linagliptin patients and in 39% of glimepiride patients. Hypoglycaemia was the most common treatment-related adverse event reported. Significantly fewer patients in the linagliptin group experienced at least one investigator-defined hypoglycaemic event compared with the glimepiride group (7.5% versus 36% respectively). Most episodes were mild to moderate in severity, however there was one event in the linagliptin group and 12 events in the glimepiride group in which patients required assistance.. [2,3] In the placebo-controlled study, hypoglycaemic events occurred in 0.6% (3/523) of linagliptin patients and in 2.8% (5/177) of placebo-treated patients. The majority of hypoglycaemic events in the placebo group occurred when patients were taking concomitant sulphonylurea rescue medication. [4]

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

Summary of clinical effectiveness issues

The submitting company has requested that SMC considers this product when positioned for use only in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control in patients for whom the addition of a sulphonylurea is inappropriate.

Neither of the key studies presented in the submission recruited patients for whom addition of a sulphonylurea was inappropriate, both study protocols included use of sulphonylureas either as the active comparator, [2,3] or as rescue medication. [4,5] A limitation of the active-comparator study is that the maximum daily dose of glimepiride was limited to 4mg, although the marketing authorisation permits use of up to 6mg daily in exceptional cases. [7] Furthermore, the European Medicines Agency considered that non-inferiority could not be concluded from the available data; the non-inferiority margin was judged to be too wide, given the treatment effects of both linagliptin and glimepiride and that approximately 50% of patients were taking less than 4mg of glimepiride. [8]

The primary outcome of the studies was a surrogate measure of glycaemic control although HbA1c is the most widely accepted measure of long-term glycaemic control and reduction is associated with a decreased risk of microvascular complications of diabetes. Treatment guidelines recommend HbA1c targets in the treatment of diabetes. [9,10]

Apart from the limitation of non-inferiority margin discussed above, in general the two studies were well designed and conducted, with little risk of bias identified, however neither used a comparator relevant to the company's proposed positioning. An indirect comparison using the Bucher methodology was undertaken in which linagliptin was compared with sitagliptin. Sitagliptin is the most commonly prescribed DPP-4 inhibitor in NHS Scotland. The results of the comparison indicated that linagliptin and sitagliptin were similar in efficacy and in safety. A limitation of the indirect comparison was that due to the choice of methodology, a number of clinical studies were excluded. If a mixed treatment comparison had been performed, then more of the published data could have been included to provide a more comprehensive comparison of linagliptin and sitagliptin.

A potential advantage of linagliptin is that it does not require dose adjustment in patients with renal impairment, whereas the other available DPP-4 inhibitors have different dosing requirements or are not recommended in moderate to severe renal failure.

Summary of comparative health economic evidence

The submitting company conducted a cost-minimisation analysis comparing linagliptin with sitagliptin for the treatment of type 2 diabetes mellitus to improve glycaemic control in adults, in combination with metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control and in patients for whom the addition of a sulphonylurea is inappropriate. A one year time horizon was selected for the base-case.

The clinical evidence used to support the assumption of equivalent efficacy between linagliptin and sitagliptin was based on two randomised, placebo controlled double-blind parallel-group studies; one compared linagliptin plus metformin to placebo plus metformin in patients with type 2 diabetes receiving metformin, and another compared sitagliptin plus metformin to placebo plus metformin in patients with type 2 diabetes with inadequate glycaemic control. As there were no head-to-head trials comparing linagliptin to sitagliptin, an indirect comparison, as described above, was used to support the economic analysis.

The analysis priced linagliptin at parity to sitagliptin and presented an annual treatment cost of £434 per patient and given the similar clinical outcomes demonstrated in the indirect comparison, linagliptin would be considered a cost-effective treatment option in the proposed patient group.

The main limitation of the analysis was that linagliptin has not been compared to pioglitazone, which is included as a treatment option along with DPP-IV inhibitors and sulphonylureas in the SIGN 116 treatment algorithm.

The economic case has been demonstrated for the comparison with sitagliptin.

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" 116 in March 2010. 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). With respect to dipeptidyl peptidase-4 (DPP-4) inhibitors, compared with placebo sitagliptin, vildagliptin and saxagliptin have been shown to be effective at lowering HbA1c by 0.7% (7.65 mmol/mol), 0.6% (6.56 mmol/mol) and 0.6% (6.56 mmol/mol) respectively. Systematic reviews have demonstrated that they are well tolerated with no severe hypoglycaemia reported in study patients taking DPP-4 inhibitors. Long-term effects are unknown. The guideline recommends that DPP-4 inhibitors may be used to improve blood glucose control in people with type 2 diabetes mellitus. In the treatment algorithm devised in the guideline, DPP-4 inhibitors, in addition to metformin, are considered an alternative second-line option to sulphonylureas in patients with type-2 diabetes; if hypoglycaemic episodes or weight gain is a concern. They are also considered a third-line option, in addition to the combination of metformin and a sulphonylurea if weight gain is a concern.

Guidance published in May 2009 by the National Institute for Health and Clinical Excellence "Type 2 Diabetes – newer agents (CG87)" made several recommendations for the DPP-4 class of anti-diabetic agents. Addition of a DPP-4 inhibitor (sitagliptin, vildagliptin) instead of a sulphonylurea as second-line therapy to first-line metformin when control of blood glucose remains or becomes inadequate can be considered if:

- the person is at significant risk of hypoglycaemia or its consequences or
- the person does not tolerate a sulphonylurea or a sulphonylurea is contraindicated.

Addition of a DPP-4 inhibitor (sitagliptin, vildagliptin) as second-line therapy to first-line sulphonylurea monotherapy when control of blood glucose remains or becomes inadequate can be considered if metformin is not tolerated or contraindicated. Sitagliptin is a third-line therapy option to first-line metformin and a second-line sulphonylurea when control of blood glucose remains or becomes inadequate and insulin is unacceptable or inappropriate. The guideline recommends that continuation of DPP-4 inhibitors beyond six-months should only be if there is a reduction of at least 0.5% in HbA1c over this time. DPP-4 inhibitors (sitagliptin, vildagliptin) may be preferable to thiazolidinediones (e.g. pioglitazone) if further weight gain would cause or worsen significant health problems, or if the thiazolidinedione is contra-indicated or not tolerated. In patients for whom DPP-4 inhibitors or thiazolidinediones are suitable, choice of treatment should be based on patient preference.

Additional information: comparators

Medicines licensed for type 2 diabetes which can be used in combination with metformin include; other DPP-4 inhibitors, thiazolidinediones, glucagon-like peptide-1 agonists, meglitinides, alpha glucosidase inhibitors, or sulphonylureas.

Cost of relevant comparators

Drug	Usual Maintenance Dose Regimen	Cost per year (£)
Linagliptin	**5mg orally once daily**	**432***
Liraglutide	0.6mg to 1.8mg once daily by subcutaneous injection	476 to 1,428
Exenatide	5 micrograms to 10 micrograms twice daily by subcutaneous injection	828
Pioglitazone	15mg to 45mg orally once daily	319 to 488
Sitagliptin	100mg orally once daily	432
Vildagliptin	50mg orally twice daily	413
Saxagliptin	5mg orally once daily	411
Nateglinide	60mg to 180mg orally three times daily	295 to 336
Acarbose	50mg to 200mg orally three times daily	85 to 311
Repaglinide	500 micrograms to 4mg orally before meals	100 to 200**
Gliclazide modified release	30 to 120mg orally once daily	36 to 144
Glipizide	2.5 to 20mg orally daily	14 to 110
Tolbutamide	500mg to 2g orally daily	26 to 103
Gliclazide	40 to 320mg orally daily	7 to 60
Glibenclamide	5 to 15mg orally once daily	13 to 39
Glimepiride	1 to 4mg orally once daily	17 to 23

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 12 September 2011 except

*linagliptin cost from company submission.

** Cost based on three meals daily (in line with nateglinide dose regimen).

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 7,985 patients in year 1, rising to 30,243 by year 5. Based on an estimated uptake of 1% in year 1 and 12% in year 5, the impact on the medicines budget impact was estimated at £32k in year 1 and £1.5m in year 5. The introduction of linagliptin is expected to be cost neutral overall as it is expected to displace sitagliptin which has the same acquisition cost.

References

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

1) Boehringer Ingelheim Limited / Eli Lilly and Company Limited. Trajenta summary of product characteristics http://www.medicines.org.uk/emc/ [last updated 21 September 2011]
2) Gallwitz B, Uhlig-Laske B, Bhattacharaya S et al. Linagliptin Has Similar Efficacy to Glimepiride But Improved Cardiovascular Safety Over 2 Years in Patients With Type 2 Diabetes Inadequately Controlled on Metformin, Poster 39-LB, 71th Scientific Sessions of the American Diabetes Association, San Diego, California, June 24–28, 2011
3) Commercial in Confidence
4) Taskinen MR, Rosenstock J, Tamminen I, Kubiak R et al. Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes, Obesity and Metabolism 2011; 13: 65-74
5) Commercial in Confidence
6) Center for Drug Evaluation and Research. Medical Review – Linagliptin. Food and Drugs Agency [online] Available from http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm [Accessed 24 August 2011]
7) Sanofi – Aventis. Amaryl summary of product characteristics. [online] Available from http://www.medicines.org.uk/emc/ [Last updated 31 March 2011]
8) European Medicines Agency. Assessment report: Trajenta [online] Available from http://www.ema.europa.eu/ [Accessed 26 October 2011]
9) Scottish Intercollegiate Guidelines Network. Management of diabetes: guideline no. 116 [online] Available from http://www.sign.ac.uk/ [Accessed 24 August 2011]
10) National Institute for Health and Clinical Excellence. Type 2 diabetes: newer agents NICE clinical guideline 87 [online] Available from http://guidance.nice.org.uk/CG87/Guidance/pdf/English [Accessed 24 August 2011]

**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*

This assessment is based on data submitted by the applicant company up to and including 11 November 2011.

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. 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.