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

linagliptin, 5mg film-coated tablets (Trajenta®) SMC No. (850/13)

Boehringer Ingelheim and Eli Lilly

11 January 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

linagliptin (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 contraindicated due to renal impairment.

as **combination therapy**

- in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products does not provide adequate glycaemic control.
- in combination with insulin with or without metformin, when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.

SMC restriction:

- as monotherapy in patients for whom both metformin and sulphonylureas are inappropriate due to contraindications or intolerance.
- as combination therapy with a sulphonylurea and metformin when diet and exercise plus dual therapy does not provide adequate glycaemic control.

Treatment with linagliptin reduces HbA1c levels significantly more than placebo when used as monotherapy or in combination with metformin and a sulphonylurea or in combination with insulin and/or metformin and/or pioglitazone. An indirect comparison demonstrated similar efficacy to another DPP-4 inhibitor.

SMC is unable to recommend the use of linagliptin in combination with insulin as the economic case has not been demonstrated.

Overleaf is the detailed advice on this product.

Chairman, Scottish Medicines Consortium

Indication

For 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 contraindicated 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 does not provide adequate glycaemic control.
- in combination with insulin with or without metformin, when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.

Dosing Information

One 5mg linagliptin tablet to be taken orally once daily.

Product availability date

October 2012

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. 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. The initial marketing authorisation for linagliptin covered (i) use as monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate and (ii) as combination therapy with metformin or with sulphonylurea and metformin. In the initial submission for this product, the company requested that SMC consider the use of linagliptin in combination with metformin only and SMC accepted its restricted use in this setting in January 2012. The marketing authorisation for linagliptin has recently been extended to include use in combination with insulin (either with or without metformin). In this current submission the company has requested SMC to consider all elements of the licensed indication other than its (previously accepted) use in combination with metformin. The company has requested that SMC reviews linagliptin when positioned for use only where a DPP-4 inhibitor is considered appropriate.

The evidence for each element of the indication is from three phase III studies. Supportive evidence is from an open label extension study, a study in renal impairment and a study in the elderly.

Monotherapy: a randomised, double-blind, controlled study[1] recruited 503 adults with type 2 diabetes who were treatment-naïve or had previously received one oral antidiabetic medicine (which was stopped six weeks prior to randomisation). Patients were required to have glycosylated haemoglobin (HbA1c) levels between 6.5 and 9.0% if pre-treated or between 7.0 and 10% if treatment-naïve. They were randomised, stratified by baseline HbA1c (<8.5% versus ≥8.5%) and by prior antidiabetic treatment status, in a ratio of 2:1 to linagliptin 5mg or placebo once daily for 24 weeks. In both treatment groups, approximately 56% of patients were treatment-naïve. The primary outcome was change from baseline in HbA1c (adjusted for baseline HbA1c and previous oral antidiabetic medicine) at 24 weeks in the full analysis set (FAS), defined as randomised patients who had received at least one dose of study medication and who had HbA1c measured at baseline and at least once during treatment. The FAS comprised 333 and 163 patients in the linagliptin and placebo groups respectively. From a mean baseline HbA1c of 8.0 in both treatment groups, the adjusted mean change at 24 weeks was -0.44 (standard error [SE] 0.05) for linagliptin and +0.25 (SE 0.07) for placebo; a difference of -0.69 (SE 0.08) (95% confidence interval [CI]:-0.85 to -0.53) (p<0.0001). At 24 weeks, linagliptin was superior to placebo for the secondary endpoint of absolute response, defined as the percentage of patients that attained target HbA1c (<7.0%): 25% (77/306) versus 12% (17/147), respectively; odds ratio (OR) 2.9, p=0.006. Longer duration of treatment produced a greater difference between linagliptin and placebo in improvement of HbA1c: −0.46% at 6 weeks to −0.69% at 24 weeks, p<0.0001.

Combination with a sulphonylurea plus metformin: a randomised, double-blind controlled study[2] recruited 1,058 adults with type 2 diabetes insufficiently controlled despite treatment with metformin (≥1,500mg/day) plus a sulphonylurea (maximum tolerated dose). Patients were required to have HbA1c levels between 7.0 and 10.0% and body-mass index (BMI) ≤40kg/m^2. They were randomised, stratified by baseline HbA1c (<8.5% versus ≥8.5%), in a ratio of 3:1, to 24 weeks of treatment with linagliptin 5mg once daily or placebo (in addition to metformin and sulphonylurea at stable doses for at least 10 weeks). Pioglitazone and (in Canada only) insulin were allowed as rescue medication. The primary outcome and analysis set were the same as in the monotherapy study described above. The FAS comprised 778 and 262 patients in the linagliptin and placebo groups respectively. Baseline HbA1c was 8.15 (SE 0.03) for linagliptin and 8.14 (SE 0.05) for placebo. At week 24, the mean adjusted change from baseline in HbA1c was -0.72 (SE 0.03) for linagliptin and -0.1 (SE 0.05) for placebo; a difference of -0.62 (SE 0.06) (95% CI: -0.73 to -0. 50) (p<0.0001). At 24 weeks, significantly more linagliptin than placebo patients achieved HbA1c <7.0% (29% versus 8.1%), OR 5.5, p<0.0001.

Combination with insulin: a randomised, double-blind controlled study[3] recruited 1,263 adults with type 2 diabetes insufficiently controlled despite treatment with subcutaneous basal insulin alone or in combination with metformin and/or pioglitazone. Patients were required to have a baseline HbA1c between 7.0% and 10.0% and a BMI ≤45kg/m^2. Following a two-week placebo controlled run-in period, patients were randomised equally to 52 weeks treatment with linagliptin 5mg orally once daily (n=633) or placebo (n=630). All patients also received basal insulin and some also received metformin and/or pioglitazone. The basal insulin dose remained stable for the first 24 weeks and then could be adjusted at the investigator's discretion. Doses of metformin and pioglitazone remained stable for the duration of the study. Randomisation was stratified by the HbA1c value (<8.5% versus ≥8.5%), renal function and concomitant use of oral antidiabetic drugs (none, metformin only, pioglitazone only, metformin plus pioglitazone).

The primary outcome was change from baseline to week 24 in HbA1c in the FAS (all randomised patients who were treated with at least one dose of study medication, had a baseline HbA1c measurement, and had at least one on-treatment HbA1c measurement within the first 24 weeks of double-blind treatment): n=618 for linagliptin and n=617 for placebo. Baseline HbA1c (SE) was 8.31 (0.03) in the linagliptin group and 8.29 (0.03) in the placebo group. The adjusted mean change from baseline in HbA1c at week 24 was -0.58% (0.08) for linagliptin and +0.07 (0.08) for placebo; a difference of -0.65 (0.05) (95% CI: -0.74 to -0.55) (p<0.0001). At 24 weeks, significantly more linagliptin than placebo patients achieved an absolute response HbA1c <7.0%: 18% (109/618) versus 7.1% (44/617), respectively.

An open-label, 78-week extension study[4] recruited 2,121 patients (1,532 patients previously on linagliptin and 589 patients previously on placebo) who had completed one of four double blind 24-week studies and received open-label linagliptin 5mg daily. The primary aim of the study was to assess safety; a secondary efficacy outcome was the HbA1c change from baseline over time. A total of 1,880 (89%) patients completed the extension study. In those randomised to linagliptin in the previous studies (group A), the treatment effect achieved during the first 24 weeks of treatment (mean change in HbA1c from baseline to week 24: -0.8%) was maintained over the 78 weeks of the extension phase (change from baseline to week 102: -0.8%). In patients randomised to placebo previously and switched to linagliptin monotherapy in the extension phase (group B), the change in mean HbA1c was -0.9% after 78 weeks. Overall, 40% of patients had missing HbA1c data at the end of the extension study. A total of 42% of patients in group A and 46% of those in group B reached the HbA1c target of <7.0% at week 78 of the extension phase.

A randomised, double-blind, controlled study[5] compared linagliptin 5mg orally once daily with placebo in 133 patients with type 2 diabetes and moderate to severe chronic renal impairment (86% of patients had baseline estimated glomerular filtration rate <30mL/minute) who continued to take their previous antidiabetic medicines. The adjusted mean difference from placebo in HbA1c after 52 weeks was -0.72% (95% CI: -1.03 to -0.41) (p<0.0001).

A randomised, double-blind, controlled study[6] compared linagliptin 5mg orally once daily (n=160) with placebo (n=78) in type 2 diabetic patients ≥70 years who were uncontrolled (HbA1c ≥7.0%) despite treatment with metformin and/or sulphonylurea and/or insulin. The primary outcome of adjusted mean change from baseline in HbA1c after 24 weeks of treatment was significant in favour of linagliptin over placebo with an estimated treatment difference of -0.64% (95% CI -0.81 to -0.48; p<0.0001).

Summary of evidence on comparative safety

There is no direct study evidence comparing linagliptin with an active comparator in the indications under review.

In the monotherapy study[1] the safety profile was similar to placebo. In the study of linagliptin combined with metformin and a sulphonylurea,[2] treatment-related adverse events occurred in 18% (142/792) of linagliptin-treated patients versus 11% (30/263) of placebo-treated patients. A total of 23 patients (2.9%) in the linagliptin arm discontinued treatment due to adverse events compared to 5 patients (1.9%) in the placebo arm. Adverse events (>5% in any group)

occurring in a higher proportion of linagliptin patients included hypoglycaemia (23% in linagliptin versus 15% in placebo-treated patients) and nasopharyngitis (5.2% versus 4.6%, respectively).

In the study of linagliptin combined with insulin[3], the safety profile was comparable with placebo. Cardiac disorders were reported for 55 patients (8.7%) in the linagliptin group and 42 patients (6.7%) in the placebo group. There were 10 deaths reported (five in each group).

In the renal impairment study, there was no major difference in the incidence of adverse events between the linagliptin and the placebo groups. The use of linagliptin in patients with severe renal insufficiency was considered acceptable by the European Medicines Agency (EMA).[5]

The study comparing linagliptin with placebo in elderly type 2 diabetic patients[6] also receiving metformin and/or sulphonylurea and/or insulin found no safety concerns. The summary of product characteristics for linagliptin notes that clinical experience in patients over 75 years of age is limited.

The summary of product characteristics for linagliptin states that there have been spontaneously reported adverse reactions of acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of linagliptin. If pancreatitis is suspected, linagliptin should be discontinued.

Summary of clinical effectiveness issues

Linagliptin has already been accepted by SMC (no: 746/11) for use in combination with metformin when diet and exercise plus metformin do not provide adequate glycaemic control, but use is restricted to patients for whom the addition of a sulphonylurea is inappropriate. In this submission, the submitting company has requested that SMC considers linagliptin when positioned for use only where a DPP-4 inhibitor is considered appropriate.

The pivotal studies demonstrated that treatment with linagliptin reduces HbA1c levels significantly more than placebo when used as monotherapy or in combination with metformin and a sulphonylurea or in combination with insulin and/or metformin and/or pioglitazone. In common with many trials of diabetes drugs, efficacy is presented as the surrogate outcome of response in HbA1c. HbA1c is a widely accepted marker but caution should be applied in interpreting such results as reduction in HbA1c may not translate into reduced microvascular or macrovascular outcomes.

As with other DPP-4 inhibitors, the risk of hypoglycaemia with linagliptin is low. Linagliptin was considered by the EMA to be weight neutral, except when combined with pioglitazone.[5]

There is no direct clinically relevant comparative study evidence versus a relevant active comparator. There are three other DPP-4 inhibitors available: sitagliptin, saxagliptin and vildagliptin. There are differences among the DPP-4 inhibitors in relation to their licensed indications and the situations in which they have been accepted for use by SMC. Sitagliptin is the most relevant comparator as the range of indications for which it is available most closely matches the indications under review for linagliptin. Sitagliptin is the most widely prescribed DPP-4 inhibitor in Scotland with a 92% market share in 2010. Current guidelines for the

treatment of type 2 diabetes place the thiazolidinedione, pioglitazone, in a similar line of therapy to DPP-4 inhibitors; however, the submitting company's proposed positioning excludes pioglitazone as a comparator.

Due to the lack of direct clinically relevant comparative study data, linagliptin was compared indirectly with sitagliptin. The indirect comparison was a model-based meta-analysis (MBMA) which used a Bayesian approach based on a Markov Chain Monte Carlo methodology to describe HbA1c levels as a function of dose, time and selected co-variates (including study design, patient population and treatment duration) with modelling for unexplained inter-patient and inter-study variations. The aim of the indirect comparison was to estimate the comparative reduction in HbA1c between linagliptin and sitagliptin irrespective of background therapy. The base case analysis included 52 studies (35 with sitagliptin and 17 with linagliptin), estimated the complete HbA1c time profile, and concluded that HbA1c lowering effects of linagliptin and sitagliptin monotherapy appeared similar, with an estimated reduction in mean HbA1c at 24 weeks of 0.720% (90% credible interval: 0.648% to 0.799%) for linagliptin 5mg daily and 0.786% (90% credible interval: 0.700% to 0.873%) for sitagliptin 100mg daily. For every treatment combination there was a numerical but not statistically significant greater mean reduction in HbA1c with sitagliptin.

These results were consistent across the background therapies modelled (triple therapy with metformin and sulphonylurea, combinations with insulin +/- metformin).

Some concerns were identified with the indirect comparison: the robustness of the search strategy; there was no assessment of the adverse event profile included in the analysis, or other outcomes relevant in type 2 diabetes, e.g. weight change; 90% rather than 95% credible intervals were used to assess similar efficacy; and the source of the linagliptin data was an internal database rather than published data as available for sitagliptin, which could have introduced bias.

As sitagliptin is not accepted for use by SMC in the combination with insulin indication, it is not considered a suitable comparator for this element of the indication in a cost minimisation analysis.

Unlike the other DPP-4 inhibitors, linagliptin requires no dosage adjustment in patients with any degree of renal impairment. Sitagliptin, saxagliptin and vildagliptin require dose reduction if renal function is moderately impaired or worse. Saxagliptin is not recommended for use in patients with end stage renal disease requiring haemodialysis.

Summary of comparative health economic evidence

The submitting company presented a simple cost-minimisation analysis over a one-year time horizon comparing linagliptin with sitagliptin for use as both monotherapy and combination therapy in patients with type 2 diabetes mellitus where a DPP-4 inhibitor is considered appropriate. The assumption of comparable efficacy of linagliptin and sitagliptin, which underpins the cost-minimisation analysis, was based on an indirect comparison.

The analysis included drug acquisition costs of linagliptin and sitagliptin only. The submitting company acknowledged that there would be costs involved relating to initiation of therapy, monitoring costs, management of adverse events and long-term complications associated with type 2 diabetes. However, as both treatments are administered orally, can be initiated in the

same setting and require similar follow-up, it is anticipated the resource use would be similar for sitagliptin and linagliptin.

The submitting company estimated the cost of both linagliptin and sitagliptin to be £434 per annum based on drug acquisition costs alone. Therefore, the company concluded that linagliptin is cost-effective on the basis of comparable efficacy with sitagliptin at equivalent cost.

The following weaknesses were identified:

- The cost-effectiveness of linagliptin in combination with insulin has not been demonstrated. As sitagliptin is not accepted for use by SMC in the combination with insulin indication, it is not considered a suitable comparator for this element of the indication in a cost minimisation analysis
- The analysis only compared linagliptin with sitagliptin on the basis that sitagliptin is the most widely used DPP-4 inhibitor in NHS Scotland. While this is an appropriate justification for the comparator treatment selected, it is noted that the cost-effectiveness of linagliptin in comparison with other DPP-4 inhibitors was not provided.
- The lack of direct trial data comparing linagliptin with sitagliptin is a weakness; however, it was considered reasonable to conclude comparable efficacy with sitagliptin.

The results indicate linagliptin and sitagliptin have comparable efficacy at equivalent price. Therefore, the economic case for linagliptin has been demonstrated when sitagliptin would be considered appropriate. However, the economic case for linagliptin when used in combination with insulin has not been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was made from Diabetes UK, Scotland.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guideline Network (SIGN) published guideline 116 Management of diabetes A National Clinical Guideline in March 2010.[7] 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 Clinical Excellence (NICE) published clinical guideline 87: Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes DPP-4 inhibitors (sitagliptin, vildagliptin) in May 2009.[8] It recommends considering the addition of a DPP-4 inhibitor as second- or third-line therapy in specific circumstances.

Additional information: comparators

Sitagliptin, saxagliptin, vildagliptin. Licensed indications for each DPP-4 inhibitor vary. The cost for pioglitazone has also been included although it is outwith the submitting company's proposed positioning.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
linagliptin	**5mg orally once daily**	**432**
sitagliptin	100mg orally once daily	432
vildagliptin	50mg orally twice daily*	413
saxagliptin	5mg orally once daily	411
pioglitazone	15 to 45mg orally once daily	86 to 139

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 6 November 2012 * dose for the indications under review.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 23,271 in year 1 rising to 27,674 in year 5, with an estimated uptake rate of 13.10% in year 1 and 22.80% in year 5. The gross impact on the medicines budget was estimated to be £1.322m in year 1 and £2.734m in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be cost neutral.

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

References

1. Del Prato S, Barnett AH, Hulsman H et al. Effect of linagliptin monotherapy on glycaemic control and markers of β-cell function in patients with inadequately controlled type-2 diabetes: a randomized controlled trial. Diabetes Obes Metab 2011; 13: 258-67.
2. Owens D, Swallow R, Dugit K, 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
3. Study 1218.36. A Phase III randomised, double-blind, placebo-controlled, parallel group efficacy and safety study of Linagliptin (5 mg), administered orally once daily for at least 52 weeks in type 2 diabetic patients in combination with basal insulin therapy. Boehringer Ingelheim Data on File, 2012
4. Gomis R, Owens DR, Taskinen MR et al. Long-term safety and efficacy of linagliptin as monotherapy or in combination with other oral glucose-lowering agents in 2121 subjects with type 2 diabetes: up to 2 years exposure in 24-week phase III trials followed by a 78-week open-label extension. The International Journal of Clinical Practice 2012; 66: 731-40
5. European Medicines Agency, European Public Assessment Report for linagliptin (Trajenta®) EMEA/H/C/002110/0000 23 June 2011
6. Study 1218.63. A Phase III randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of linagliptin (5 mg), administered orally once daily over 24 weeks in type 2 diabetic patients (age >70 years) with insufficient glycaemic control (HbA1c ≥7.0%) despite metformin and/or sulphonylurea and/or insulin therapy. Boehringer Ingelheim Data on File, 2011
7. Scottish Intercollegiate Guidelines Network. Management of Diabetes: A national clinical guideline. March 2010; Publication No 116 (SIGN 116).
8. National Institute for Health and Clinical Excellence, Type 2 Diabetes: Management of Type 2 Diabetes (Clinical Guideline 87), 2009.

This assessment is based on data submitted by the applicant company up to and including 14 December 2012.

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.