Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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Re-Submission

linagliptin 5mg tablet (Trajenta®) SMC No. (850/13)

Boehringer Ingelheim and Eli Lilly

10 April 2015

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 re-submission

linagliptin (Trajenta®) is accepted for use within NHS Scotland.

Indication under review: the treatment of type 2 diabetes mellitus to improve glycaemic control in adults in combination with insulin with or without metformin, when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.

Linagliptin, compared with placebo, improved glycaemic control in adults with type 2 diabetes who had inadequate glycaemic control on an insulin-containing regimen.

SMC has previously accepted linagliptin for restricted use as monotherapy in combination with metformin, and in combination with a sulphonylurea and metformin, This now extends the advice to include its use in combination with insulin.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 11 May 2015

Indication

Treatment of type 2 diabetes mellitus to improve glycaemic control in adults in combination with insulin with or without metformin, when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.

Dosing Information

5mg orally once daily.

Product availability date

24 October 2012

Summary of evidence on comparative efficacy

Linagliptin is one of five dipeptidyl peptidase-4 (DPP-4) inhibitors marketed in the UK for type 2 diabetes.[1] SMC has previously issued advice for linagliptin as monotherapy, as dual therapy in combination with metformin, and as triple therapy in combination with a sulphonyurea and metformin[2,3] This resubmission relates to use in combination with insulin.

A double-blind phase III study (1218.36) recruited adults who had type 2 diabetes with inadequate glycaemic control, defined as glycosylated haemoglobin (HbA1c) ≥7.0% (but ≤10%), on basal insulin ± metformin ± pioglitazone. Randomisation was stratified by HbA1c (<8.5% versus ≥8.5%), renal function (estimated glomerular filtration rate) and concomitant oral anti-diabetic drugs (OADs) (metformin only; pioglitazone only; metformin plus pioglitazone; or none) and patients were assigned equally to linagliptin 5mg orally once daily or placebo for at least 52 weeks. For the initial 24 weeks, the doses of background insulin could not be changed. After this, it could be adjusted at the discretion of the investigator to achieve fasting plasma glucose (FPG) ≤6.1mmol/L (110mg/dL). No change was permitted to the dose of concomitant OADs. The primary outcome, change from baseline to week 24 in HbA1c, was analysed using an analysis of covariance (ANCOVA) that included treatment, concomitant OAD and renal function as fixed effects and baseline HbA1c as linear covariate, with last observation carried forward (LOCF) for missing data. This was assessed in the full analysis set, which comprised all randomised patients who received at least one dose of study medication and had a baseline and at least one on-treatment HbA1c measurement. Linagliptin, compared to placebo, significantly reduced adjusted mean HbA1c from baseline to week 24: -0.58% versus 0.07%, with a difference of -0.65% (95% confidence interval [CI]: -0.74% to -0.55%). Similar figures were observed at week 52: -0.48% versus 0.05%, with a difference of -0.53% (95% CI: -0.64% to -0.43%). At 52 weeks, significantly more patients in the linagliptin group, compared to the placebo group, had a reduction of at least 0.5% in HbA1c from baseline: 37% versus 17%, p<0.0001. Also, at 52 weeks among patients with baseline HbA1c ≥7.0%, in the linagliptin and placebo groups, respectively, 16% and 7% achieved the HbA1c target of <7.0%, p<0.001.[4,5]

A phase III double-blind study (1218.43) recruited 133 adults with type 2 diabetes and renal impairment, defined as glomerular filtration rate <30mL/minute (not on regular dialysis), and who had inadequate glycaemic control (HbA1c ≥7.0%) on insulin and/or sulphonylurea. A subgroup of 54 and 55 patients within the linagliptin and placebo groups, respectively, had insulin as part of their background therapy. Within this subgroup, change from baseline to 12 weeks in adjusted mean HbA1c was -0.44% in the linagliptin group and -0.01% in the placebo group, with a between group difference of -0.43% (95% CI: -0.75% to -0.11%).[5]

A phase III double-blind study (1218.63) in patients with type 2 diabetes aged at least 70 years with inadequate glycaemic control (HbA1c ≥7.0%) on metformin ± sulphonylurea ± insulin compared linagliptin 5mg once daily for 24 weeks with placebo. There were 35 and 15 patients in the linagliptin and placebo groups who were receiving insulin as part of their background therapy. In the European Medicines Agency (EMA) review, data from these patients were combined with data from 91 and 106 patients in the pivotal study (1218.36) who were aged at least 70 years. Within this combined group, change from baseline to 24 weeks in HbA1c was -0.68% and 0.09% in the linagliptin and placebo groups, respectively, with a between treatment difference of -0.77% (95% CI: -0.95% to -0.59%).[5]

Summary of evidence on comparative safety

The adverse event profile of linagliptin is well characterised and similar to that of other DPP-4 inhibitors. In the pivotal study (1218.36), within the respective linagliptin and placebo groups there were similar rates of: adverse events, 78% and 81%; drug-related adverse events, 19% and 22%; severe adverse events 8.2% and 8.3%; and adverse events leading to discontinuation of study drug, 3.3% and 4.4%. Over the initial 24 weeks within the respective groups, there were similar rates of: hypoglycaemia, 22% and 23%; symptomatic hypoglycaemia associated with plasma glucose ≤4mmol/L, 17% and 19%; and ≤3mmol/L, 8.6% and 8.7%; and severe hypoglycaemia, 0.3% and 0.6%. Over the whole study period there were also similar rates of: hypoglycaemia, 31% and 32%; symptomatic hypoglycaemia associated with plasma glucose ≤4mmol/L, 24% and 25%; and ≤3mmol/L, 14% and 14%; and severe hypoglycaemia, 1.7% and 1.1%. There was no significant change from baseline in mean body weight at 24 weeks, -0.16kg with linagliptin and 0.12kg with placebo, or at 52 weeks, -0.3kg with linagliptin and -0.04kg with placebo. An analysis of this study in which the rate of adverse events in the first 24 weeks was compared to the total study period indicated that long-term treatment with linagliptin in patients on basal insulin therapy did not lead to clinically relevant increases in particular adverse events.[4,5]

In the pivotal study, the rate of adjudicated cardiovascular events (cardiovascular death, myocardial infarction, stroke or hospitalisation due to unstable angina) was numerically higher in the linaglitptin group, compared with the placebo group: 2.9% and 1.7%, respectively. However, in an updated meta-analysis of all linagliptin studies, adjudicated events occurred at similar rates in the linagliptin group and comparator group (placebo and active comparators): 1.06% and 1.65%, with a Cox regression hazard ratio of 0.83 (95% CI: 0.57 to 1.21).[5]

Summary of clinical effectiveness issues

Linagliptin is one of five DPP-4 inhibitors marketed in the UK, all of which are indicated for use in combination with insulin ± metformin. Saxagliptin was recently accepted (in November 2014) by SMC for use in this indication. SMC has not received submissions for the other DPP-4 inhibitors for use in combination with insulin. Other third-line anti-diabetic medicines licensed for use in combination with insulin include the glucagon-like peptide-1 (GLP-1) agonists, exenatide, lixisenatide and liraglutide; the sodium-glucose co-transporter 2 (SGLT-2) inhibitors, dapagliflozin, canagliflozin and empagliflozin; and the thiazolidinedione (TDZ), pioglitazone. All of these have been accepted by SMC for use in combination with insulin.[6-14]

In the pivotal study, the primary outcome was HbA1c, an established measure of glucose control over the preceding two to three months that has been shown in large well-controlled studies to be linked to risk of diabetic complications. There are no long-term outcome data for linagliptin in combination with insulin. In the UK, HbA1c results are expressed in mmol/mol rather than as a percentage. The equivalent of the HbA1c targets of 6.5% and 7.5% are 48mmol/mol and 58mmol/mol.

In the pivotal study, HbA1c was significantly reduced with linagliptin compared to placebo. The European Medicines Agency noted that efficacy of linagliptin as add-on to insulin was modest but statistically significant and clinically relevant.[5] At 52 weeks, 37% of those receiving linagliptin had achieved a reduction in HbA1c of at least 0.5% compared with 17% in the placebo group, and 16% had achieved HbA1c of 7.0% or lower compared with 7% in the placebo group.[4]

A Bayesian network meta-analysis (NMA) was conducted in adults with type 2 diabetes that was uncontrolled despite diet, exercise and an insulin-containing regimen as background anti-diabetic therapy. This compared linagliptin with the GLP-1 agonists, exenatide and lixisenatide, and the SGLT-2 inhibitors, dapagliflozin, canagliflozin and empagliflozin, for the outcomes of change from baseline in HbA1c, body weight and systolic blood pressure (SBP) and risks of overall, non-severe and severe hypoglycaemia and urinary tract infection at 24 weeks. From this analysis, the submitting company concluded that overall linagliptin is broadly equivalent to these other anti-diabetic medicines in terms of efficacy and safety. However, it was noted that for weight and SBP there was a trend suggesting that the SGLT-2 inhibitors and GLP-1 agonists were superior to linagliptin, although the differences may not be clinically significant. The internal validity is limited by heterogeneity across the studies in terms of design, baseline characteristics, timeframe for assessment of outcomes, definitions of adverse event outcomes and magnitude of outcomes in the common control, placebo, groups. Also, the presentation of results for some outcomes was unclear.

Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis comparing linagliptin to SGLT-2 inhibitors including dapagliflozin, canagliflozin and empagliflozin, and GLP-1 agonists including exenatide and lixisenatide. The analysis was based on a one year time horizon. Expert responses have indicated that DPP-4 inhibitors are the treatments most likely to be displaced in Scotland. However, the only DPP-4 inhibitor that has been accepted by SMC for use in combination with insulin is saxagliptin, and as this was only recently accepted by SMC in November 2014, it was not considered to be an appropriate comparator. The comparison with SGLT-2 and GLP-1 agonists was, therefore, considered to be appropriate.

There is no direct head to head evidence comparing linagliptin to SGLT-2 inhibitors or GLP-1 agonists. Therefore, a NMA was used to estimate comparative efficacy for clinically relevant outcomes. Some weaknesses were identified with the analysis as noted above, including inconsistencies within the presented data. Despite these limitations, on balance, the results of the NMA support the conclusion that linagliptin has comparable efficacy to the SGLT-2 inhibitors and GLP-1 agonists for the outcome of mean change in baseline HbA1c from 0 to 24 weeks and other clinically important outcomes.

Only drug costs were included in the analysis. As linagliptin and SGLT-2 inhibitors are oral antidiabetic treatments provided in the same setting requiring similar follow up, no other resource use was included. In relation to the comparison with GLP-1 agonists, the costs of needles and staff training were not included in the analysis, which may be conservative.

The submitting company estimated that linagliptin resulted in a total annual cost of £433 and was considered cost-saving versus SGLT-2 inhibitors and GLP-1 agonists, resulting in incremental savings of between £43 and £395 per year. Given the simplicity of the analysis, no sensitivity analysis was conducted.

Despite some concerns regarding the relevance and appropriateness of comparators, overall the analysis was considered to be reasonable. Therefore, the economic case has been demonstrated.

Summary of patient and public involvement

A Patient 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. The treatment algorithm notes several options for third-line treatment of type 2 diabetes mellitus to be added in combination with metformin and/or sulphonylurea; additional oral anti-diabetic drugs, pioglitazone or DPP-4 inhibitors; or injections of GLP-1 agonists or commencement of insulin. It is noted that these should only be continued if either the patient's individualised target is achieved or HbA1c falls >0.5% (5.5 mmol/mol) in 3-6 months.[15]

The National Institute for Health and Care Excellence (NICE) published Clinical Guideline 87 – The management of type 2 diabetes - newer agents in May 2009.[16]

Additional information: comparators

Comparators include other DPP-4 inhibitors, e.g. alogliptin, sitagliptin, saxagliptin and vildagliptin, and other third-line anti-diabetic medicines such as TDZ, e.g. pioglitazone, GLP-1 agonists, e.g. exenatide, lixisenatide and liraglutide, and SGLT-2 inhibitors, e.g. canagliflozin, dapagliflozin and empagliflozin.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
DPP-4 inhibitors		
Linagliptin	**5mg orally once daily**	**432**
Sitagliptin	100mg orally once daily	432
Vildagliptin	50mg orally twice daily	413
Saxagliptin	5mg orally once daily	411
Alogliptin	25mg orally once daily	346
SGLT-2 inhibitors		
Canagliflozin	100mg to 300mg orally once daily	475 to 606
Dapagliflozin	10mg orally once daily	476
Empagliflozin	10mg to 25mg orally once daily	476
GLP-1 agonists		
Liraglutide	1.2mg to 1.8mg SC once daily	952 to 1,428
Exenatide	10microgram SC twice daily	828
Lixisenatide	20microgram SC once daily	704
TDZ		
Pioglitazone	15mg to 45mg orally once daily	17 to 23

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 03 January 2015. SC = subcutaneous injection.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 45,069 in year one rising to 51,846 in year five, with an estimated uptake rate of 5% in all years. The gross impact on the medicines budget was estimated to be £841k in year 1 and £968k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to result in savings of £40k in year 1, rising to £46k in year 5.

References

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

1. Boehringer Ingelheim. Summary of product characteristic for Trajenta, accessed 21.1.15

2. Scottish Medicines Consortium. Advice number 746/11, linagliptin,

3. Scottish Medicines Consortium. Advice number 850/13, linagliptin,

4. Yki-Jarvinen H, Rosenstock J, Duran-Garcia S et al. Effects of adding linagliptin to basal insulin regimen for inadequately controlled type 2 diabetes: a ≥ 52-week randomized, double-blind study. Diabetes Care 2013; 36(12):3875-3881.

5. European Medicines Agency. European public assessment report for linagliptin, CHMP assessment report EMA/CHMP/508574/2012, 20 September 2012.

6. Scottish Medicines Consortium. Advice number 772/12, saxagliptin, published November 2014

7. Scottish Medicines Consortium. Advice number 875/13, vildagliptin, published May 2013

8. Scottish Medicines Consortium. Advice number 607/10, sitagliptin, published July 2010

9. Scottish Medicines Consortium. Advice number 963/14, canagliflozin, published June 2014

10. Scottish Medicines Consortium. Advice number 799/12, dapagliflozin, published July 2014

11. Scottish Medicines Consortium. Advice number 993/14, empagliflozin, published October 2014

12. Scottish Medicines Consortium. Advice number 785/12, exenatide, published June 2012

13. Scottish Medicines Consortium. Advice number 903/13, lixisenatide, published September 2013

14. Scottish Medicines Consortium. Advice number 399/07, pioglitzone, published September 2007

15. Scottish Intercollegiate Guidelines Network (SIGN). Publication number 116; Management of diabetes, March 2010

16. National Institute for Health and Care Excellence (NICE). Clinical Guideline 87; The management of type 2 diabetes - newer agents in May 2009

This assessment is based on data submitted by the applicant company up to and including 10 February 2015.

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.