Type 2 diabetes: alogliptin

Evidence summary

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Overview

> The content of this evidence summary was up-to-date in May 2013. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

When added to certain dual and triple therapy regimens, the dipeptidyl peptidase-4 (DPP-4) inhibitor, alogliptin, reduces glycated haemoglobin (HbA1c) levels by around 5.5 mmol/mol compared with placebo. However, there are no published RCTs of alogliptin added to metformin and a sulfonylurea, or alogliptin compared with other DPP-4 inhibitors or glucagon-like peptide-1 (GLP-1) mimetics. No serious safety concerns have emerged so far; however, there are no long-term safety data and no data on the effect of alogliptin on the long-term complications of type 2 diabetes.

Effectiveness	Safety
• Alogliptin as add-on therapy reduces HbA1c by around 5.5 mmol/mol (0.5%) compared with placebo (4 RCTs of dual therapy lasting 26 weeks, 2 RCTs of triple therapy lasting 26 and 52 weeks).	• No serious safety concerns have emerged so far. • Proportionally more hypoglycaemia and drug-related skin and subcutaneous disorders with alogliptin triple therapy compared with dual therapy, but statistical significance not reported (1 RCT of 52 weeks).
Patient factors	**Cost**
• Once-daily oral dosage regimen. • Tolerability appears similar to other oral blood glucose-lowering drugs (around 2% to 4% reported adverse effects leading to discontinuation in 2 RCTs of 26 and 52 weeks).	• The cost of alogliptin is not yet known. • The 28-day drug cost for the DPP-4 inhibitors currently available ranges from £31.60 to £33.26.

Key points from the evidence

Alogliptin is a DPP-4 inhibitor that aims to lower blood glucose levels.

A submission for a marketing authorisation for alogliptin benzoate (brand name Vipidia) was made to the European Medicines Agency in May 2012. It is anticipated that alogliptin will be launched in the UK in the fourth quarter of 2013. The proposed indication is to improve glycaemic control in adults with type 2 diabetes mellitus in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, have not provided adequate glycaemic control.

This evidence summary is based on 2 randomised controlled trials (RCTs) that provide published evidence on the use of alogliptin to treat people with type 2 diabetes in line with current use of DPP-4 inhibitors in UK clinical practice. In these trials, alogliptin was added to existing metformin monotherapy for 26 weeks (dual therapy; Nauck et al. 2009) or used in combination with metformin and pioglitazone for 52 weeks (triple therapy; Bosi et al. 2011). Four other published placebo-controlled RCTs that investigated the efficacy of alogliptin added to other blood glucose-lowering drugs in dual or triple therapy for 26 weeks are discussed briefly in the Evidence review.

Across the 6 RCTs, using alogliptin 12.5 mg or 25 mg once daily as add-on therapy to a range of concurrent treatment options led to an additional reduction in HbA1c of about 5.5 mmol/mol (0.5 percentage points) compared with placebo.

Alogliptin appeared well tolerated in the 2 RCTs reviewed in this evidence summary, with most adverse events reported to be of mild or moderate intensity. The proportions of patients experiencing serious adverse events or adverse events leading to study drug discontinuation were low across all groups. In Bosi et al. (2011), hypoglycaemia was reported by proportionally more patients on alogliptin triple therapy (4.5% [18/404]) compared with dual therapy (1.5% [6/399]), as were drug-related skin and subcutaneous disorders (5.2% [21/404] with triple therapy compared with 2.3% [9/399] with dual therapy) but statistical significance was not reported.

The NICE clinical guideline on type 2 diabetes: the management of type 2 diabetes, published in 2009, included the only 2 DPP-4 inhibitors licensed at the time the guideline was developed: sitagliptin and vildagliptin. Since then, 2 further DPP-4 inhibitors have been licensed in the UK: saxagliptin and linagliptin. All 4 currently available DPP-4 inhibitors (but not alogliptin) will be included in an update of this guideline, the publication date of which is still to be confirmed.

Local decision makers will need to consider the available evidence on efficacy and safety, as well as cost and individual patient factors, when making decisions about using alogliptin.

Key evidence

Nauck MA, Ellis GC, Fleck PR et al. (2009) Efficacy and safety of adding the dipeptidyl peptidase-4 inhibitor alogliptin to metformin therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a multicentre, randomised, double-blind, placebo-controlled study. The International Journal of Clinical Practice 63: 46–55

Bosi E, Ellis GC, Wilson CA et al. (2011) Alogliptin as a third oral antidiabetic drug in patients with type 2 diabetes and inadequate glycaemic control on metformin and pioglitazone: a 52-week, randomized, double-blind, active-controlled, parallel-group study. Diabetes, Obesity and Metabolism 13: 1088–96

Update

The following information has become available since this ESNM was produced.

January 2014: Availability of alogliptin

Alogliptin has been launched in the UK as Vipidia (alogliptin benzoate) and Vipdomet (metformin hydrochloride plus alogliptin benzoate). The cost of Vipidia (excluding VAT, all strengths) is £26.60 for 28 tablets. The cost of Vipdomet (excluding VAT) is £26.60 for 56 tablets. Costs taken from MIMS, September 2014.

October 2013: Study finds no benefit from alogliptin on cardiovascular outcomes in people with a recent acute coronary syndrome

A large randomised controlled trial (EXAMINE) has found that adding alogliptin to other blood-glucose-lowering medication did not reduce the risk of cardiovascular events in people with type 2 diabetes who had had a recent acute coronary syndrome, over a median of 18 months. This study was summarised in a medicines evidence commentary.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

Relevance to NICE guidance programmes

The NICE clinical guideline on type 2 diabetes, published in 2009, is currently being updated. The final scope for this update specifies that the marketing authorisation for alogliptin is not anticipated in time for inclusion within the guideline, so alogliptin will not be included in this update.

Introduction

The NICE clinical guideline on type 2 diabetes states that the management of type 2 diabetes is complex. It involves an individualised, multifactorial approach that addresses blood pressure, blood lipids and lifestyle issues, as well as blood glucose. Controlling blood glucose requires a careful balance between the intensity of the treatment regimen and avoiding hypoglycaemia (MeReC Bulletin on type 2 diabetes [March 2012], Medicines Evidence Commentary on type 2 diabetes [September 2012]). The NICE clinical guideline recommends that patients should be involved in setting their individualised HbA1c target level, which may be above the general target of 48 mmol/

mol (6.5%), and that pursuing highly intensive management to HbA1c levels below 48 mmol/mol (6.5%) should be avoided.

Alogliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor. The NICE clinical guideline on type 2 diabetes, published in 2009, included the only 2 DPP-4 inhibitors that were licensed when the guideline was developed: sitagliptin and vildagliptin. Since then, 2 further DPP-4 inhibitors have been licensed in the UK: saxagliptin and linagliptin. All 4 currently available DPP-4 inhibitors (but not alogliptin) will be included in an update of this guideline. The current NICE clinical guideline on type 2 diabetes recommends the following relating to the use of DPP-4 inhibitors:

- Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose remains or becomes inadequate (HbA1c ≥6.5% [≥48 mmol/mol], or other higher level agreed with the individual) if:

  – the person is at significant risk of hypoglycaemia or its consequences (for example, older people and people in certain jobs [for example, those working at heights or with heavy machinery] or people in certain social circumstances [for example, those living alone]), or

  – the person does not tolerate a sulfonylurea or a sulfonylurea is contraindicated.

- Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose remains or becomes inadequate (HbA1c ≥6.5% [≥48 mmol/mol], or other higher level agreed with the individual) if:

  – the person does not tolerate metformin, or metformin is contraindicated.

- Consider adding sitagliptin[1] as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥7.5% [≥58 mmol/mol] or other higher level agreed with the individual) and insulin is unacceptable or inappropriate[2].

- Only continue DPP-4 inhibitor therapy (sitagliptin, vildagliptin) if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points [5.5 mmol/mol] in HbA1c in 6 months).

- Discuss the potential benefits and risks of treatment with a DPP-4 inhibitor (sitagliptin, vildagliptin) with the person to enable them to make an informed decision.

- A DPP-4 inhibitor (sitagliptin, vildagliptin) may be preferable to a thiazolidinedione (pioglitazone) if:

- further weight gain would cause or exacerbate significant problems associated with a high body weight, or

- a thiazolidinedione (pioglitazone) is contraindicated, or

- the person has previously had a poor response to, or did not tolerate, a thiazolidinedione (pioglitazone).

- There may be some people for whom either a DPP-4 inhibitor (sitagliptin, vildagliptin) or a thiazolidinedione (pioglitazone) may be suitable and, in this case, the choice of treatment should be based on patient preference.

See the NICE pathway on diabetes for further information.

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[1] At the time of NICE publication, sitagliptin was the only DPP-4 inhibitor with UK marketing authorisation for use in this combination.

[2] Because of employment, social or recreational issues related to putative hypoglycaemia, injection anxieties, other personal issues or obesity.

Product overview

Drug action

Alogliptin is an oral selective inhibitor of dipeptidyl peptidase-4 (DPP-4). These medicines are thought to work by enhancing the levels of active incretin hormones, which enhance insulin and reduce glucagon secretions, thereby reducing blood glucose levels.

Proposed therapeutic indication

The manufacturer (Takeda Pharmaceutical Company Limited) applied to the European Medicines Agency for a licence to market alogliptin benzoate (Vipidia) in May 2012. The proposed indication is to improve glycaemic control in adults aged 18 years and older with type 2 diabetes mellitus in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control. It is anticipated that alogliptin will be launched in the UK in the fourth quarter of 2013 (Takeda UK Ltd: personal communication May 2013).

The manufacturer has also applied for 2 other licences: for alogliptin benzoate and metformin hydrochloride fixed-dose combination (Vipdomet), and for alogliptin benzoate and pioglitazone hydrochloride fixed-dose combination (Incresync). This evidence summary does not cover these combination products.

Course and cost

The proposed usual dosage of alogliptin is 25 mg once daily. Other proposed dosages are alogliptin 12.5 mg once daily for people with moderate renal impairment or 6.25 mg once daily for people with severe renal impairment and end-stage renal disease (Takeda UK Ltd: personal communication February 2013).

Alogliptin will be available as 25 mg, 12.5 mg, and 6.25 mg tablets in 28-tablet packs. The NHS list price is yet to be determined (Takeda UK Ltd: personal communication February 2013).

Evidence review

This evidence review is based on the 2 randomised controlled trials (RCTs) that provide published evidence on the use of alogliptin to treat people with type 2 diabetes in line with current use of DPP-4 inhibitors in UK clinical practice. The first RCT investigated adding alogliptin or placebo to existing metformin monotherapy (Nauck et al. 2009). The second RCT investigated alogliptin in combination with metformin and pioglitazone (triple therapy) compared with metformin and pioglitazone (dual therapy) (Bosi et al. 2011). Key efficacy and safety outcomes are reported in table 1 for Nauck et al. (2009) and table 2 for Bosi et al. (2011).

Several other placebo-controlled RCTs have been published that investigated the efficacy of alogliptin added to other blood glucose-lowering drugs in dual or triple therapy. Four of these RCTs are discussed briefly for context in the clinical effectiveness section and the primary outcome results are summarised in table 3.

HbA1c results were reported in percentages in these studies. Percentage values have been converted to mmol/mol throughout this evidence summary using the following formula to convert DCCT (Diabetes Control and Complications Trial) units to newer IFCC (International Federation of Clinical Chemistry) units: IFCC HbA1c (mmol/mol)=[DCCT HbA1c (%)−2.15]×10.929. This means that in the range HbA1c 4% to 10%, a 1% fall in DCCT HbA1c is approximately equal to an 11 mmol/mol fall in IFCC HbA1c.

Nauck et al. (2009)

- Design: 26-week, international, multicentre, randomised, double-blind, placebo-controlled study.

- Population: 527 adults (mean age 55 years, 50.3% male) with type 2 diabetes and inadequate glycaemic control (HbA1c 7.0% [53 mmol/mol] to 10% [86 mmol/mol] inclusive) while on metformin (≥1500 mg). At baseline, mean HbA1c was 7.9% (59 mmol/mol) to 8.0% (64 mmol/mol), mean body mass index (BMI) was 32 kg/m^2, mean duration of diagnosed diabetes was 6 years, and mean metformin dose was 1847 mg per day. People taking any antidiabetic medication other than metformin were excluded from the study.

- Intervention and comparison: 2-week screening period followed by a 4-week stabilisation period on metformin (≥1500 mg or maximum tolerated dose) and single-blind placebo for alogliptin. After this, the stabilised open-label dose of metformin was continued, and patients were randomised to receive 26 weeks of double-blind treatment (in a 1:2:2 ratio) with:

    - placebo (Met+placebo),

    - alogliptin 12.5 mg once daily (Met+Alo12.5),or

    - alogliptin 25 mg once daily (Met+Alo25).

- Outcome: the primary outcome was change in HbA1c from baseline to week 26 for the modified intention-to-treat population. Secondary outcomes included change from baseline in fasting plasma glucose (FPG), fasting C-peptide, proinsulin, insulin and proinsulin/insulin ratio, and body weight; incidence of marked hyperglycaemia (FPG ≥11.1 mmol/l) and hyperglycaemic rescue; and clinical response, as measured by the incidence of HbA1c of 6.5% (48 mmol/mol) or less or 7.0% (53 mmol/mol) or less, and incidence of HbA1c decrease from baseline of at least 0.5% (5.5 mmol/mol) or at least 1.0% (11 mmol/mol) at week 26.

Table 1 Summary of Nauck et al. (2009)

	Met+Placebo	Met+Alo12.5	Met+Alo25	Analysis
Efficacy[a]	n=104	n=213	n=210	

Primary outcome: LS mean change in HbA1c from baseline to week 26 (SE)	−0.1% (0.1) points [1.1 mmol/mol] from baseline of 8.0% [64 mmol/mol]	−0.6% (0.1) points [6.6 mmol/mol] from baseline of 7.9% [63 mmol/mol]	−0.6% (0.1) points [6.6 mmol/mol] from baseline of 7.9% [63 mmol/mol]	Statistically significantly greater reduction with Alo12.5 versus placebo and Alo25 versus placebo (both p<0.001) Difference: 0.5% [5.5 mmol/mol] for both
Selected secondary outcomes:				
LS mean change in FPG from baseline to week 26 (SE)	0.0 mmol/l (0.2) from baseline of 10.0 mmol/l	−1.0 mmol/l (0.1) from baseline of 9.3 mmol/l	−1.0 mmol/l (0.1) from baseline of 9.5 mmol/l	Statistically significantly greater reduction with Alo12.5 versus placebo and Alo25 versus placebo (both p<0.001)
Patients achieving HbA1c ≤7.0% [53 mmol/mol] at week 26	18% (19/104)	52% (110/213)	44% (92/207)	Alo12.5 versus placebo p<0.001 Alo25 versus placebo p<0.001
Patients achieving HbA1c ≤6.5% [48 mmol/mol] at week 26	4% (4/104)	20% (42/213)	17% (36/207)	Alo12.5 versus placebo p=0.037 Alo25 versus placebo p=0.013
LS mean difference in body weight versus placebo at week 26 (95% CI)		0.0kg (−0.7 to 0.7)	−0.3kg (−0.9 to 0.4)	NS, both alogliptin groups versus placebo

Patients needing hyperglycaemic rescue[b] over 26-week period	24% (25/104)	9% (19/213)	8% (17/207)	Alo12.5 versus placebo p=0.004 Alo25 versus placebo p=0.003
Safety[c]	n=104	n=213	n=210	
Patients reporting at least 1 adverse event	66% (69/104)	63% (134/213)	57% (118/210)	No statistical testing reported
Patients reporting at least 1 serious adverse event	4% (4/104)	3% (6/213)	4% (8/210)	No statistical testing reported
Patients reporting adverse events leading to discontinuation	1% (1/104)	3% (7/213)	2% (4/210)	No statistical testing reported
Patients experiencing any hypoglycaemia	3% (3/104)	1% (2/104)	0	No statistical testing reported

Notes: HbA1c conversions used the formula: IFCC HbA1c (mmol/mol)=[DCCT HbA1c (%)−2.15]×10.929

Abbreviations: Alo12.5, alogliptin 12.5 mg; Alo25, alogliptin 25 mg; CI, confidence interval; FPG, fasting plasma glucose; LS, least square; Met, metformin ≥1500 mg or maximum tolerated dose; n, number of participants; NS, not statistically significant; SE, standard error.

[a] Modified intention-to-treat population: all randomised participants who had a baseline assessment and at least 1 post-baseline assessment using last observation carried forward to account for missing data.

[b] Rescue therapy for hyperglycaemia was initiated if FPG levels fell outside of pre-specified thresholds at different time points throughout the study.

[c] Modified intention-to-treat population: all randomised participants who had taken at least 1 dose of double-blind study drug.

Bosi et al. (2011)

- Design: 52-week, international, multicentre, randomised, double-blind, active-controlled study of non-inferiority and superiority.

- Population: 803 adults (mean age 55.1 years, 51.6% male) with type 2 diabetes and inadequate glycaemic control (HbA1c 7.0% [53 mmol/mol] to 10.0% [86 mmol/mol] inclusive) while on metformin (≥1500 mg or maximum tolerated dose) and pioglitazone 30 mg. At baseline, mean BMI was 31.6 kg/m^2, mean duration of diabetes was 7.2 years, and median metformin use was 1700 mg per day. Mean HbA1c was 8.1% (65 mmol/mol) to 8.3% (67 mmol/mol) for the per-protocol population at baseline.

- Intervention and comparison: before randomisation, patients already taking metformin and pioglitazone 30 mg underwent a 4-week stabilisation phase. Those using metformin and a different oral antidiabetic (excluding pioglitazone 30 mg or 45 mg or DPP-4 inhibitors) underwent a 12-week switching period to metformin and pioglitazone 30 mg before entering the same 4-week stabilisation phase. After this, the stabilised open-label dose of metformin (≥1500 mg daily or maximum tolerated dose) and pioglitazone 30 mg daily was continued and patients were randomised to receive 52 weeks of double-blind treatment (in a 1:1 ratio) with:

    – alogliptin 25 mg and pioglitazone placebo once daily (Met+Pio30+Alo25) or

    – alogliptin placebo and pioglitazone 15 mg once daily (Met+Pio45).

- Outcome: the primary outcome was change from baseline in HbA1c at 26 and 52 weeks for the per-protocol population. Secondary outcomes included: change from baseline in FPG, fasting

proinsulin/insulin ratio, C-peptide, homeostasis model assessment of beta-cell function, homeostasis model assessment of insulin resistance, body weight, serum triglycerides, cholesterol and free fatty acids; proportion of patients achieving HbA1c reductions of 6.5% (48 mmol/mol) or less or 7.0% (53 mmol/mol) or less at week 52; and incidence of hyperglycaemic rescue.

Table 2 Summary of Bosi et al. (2011)

	Met+ Pio30+ Alo25	Met+ Pio45	Analysis
Randomised[a]	n=404	n=399	
Efficacy[b]	n=303	n=306	
Co-primary outcome: LS mean change in HbA1c from baseline to week 26 (SE)	−0.89% points [−9.7 mmol/mol] from baseline of 8.3% [67 mmol/mol] (not reported)	−0.42% points [−4.6 mmol/mol] from baseline of 8.1% [65 mmol/mol] (not reported)	Statistically significantly greater decrease from baseline seen with Met+Pio30+Alo25 versus Met+Pio45, p<0.001 LS mean difference −0.47% (97.5% CI −∞ to −0.35%), non-inferior[c]
Co-primary outcome: LS mean change in HbA1c from baseline to week 52 (SE)	−0.70% [−7.7 mmol/mol] (not reported)	−0.29% [−3.2 mmol/mol] (not reported)	Statistically significantly greater decrease from baseline seen with Met+Pio30+Alo25 versus Met+Pio45, p<0.001 LS mean difference −0.42% (97.5% CI −∞ to −0.28%), non-inferior[c] and superior[d]
Selected secondary outcomes[e]:			
LS mean change in FPG from baseline to week 52 (SE)	−0.8 mmol/l from baseline of 9.0 mmol/l (not reported) n=399	−0.2 mmol/l from baseline of 9.0 mmol/l (not reported) n=396	Statistically significantly greater decrease from baseline seen with Met+Pio30+Alo25 versus Met+Pio45, p<0.001

Patients achieving HbA1c levels ≤7.0% [53 mmol/mol] at week 52	33.2% (patient numbers not reported)	21.3% (patient numbers not reported)	p<0.001
Patients achieving HbA1c levels ≤6.5% [48 mmol/mol] at week 52	8.7% (patient numbers not reported)	4.3% (patient numbers not reported)	p<0.001
LS mean change in weight from baseline to week 52 (SE)	1.10 kg (0.194) n=395	1.60 kg (0.194) n=394	NS, LS mean difference −0.50 kg (95% CI −0.13 to 0.04), p=0.071
Patients needing hyperglycaemic rescue[f] over 52-week period	10.9% (44/404)	21.8% (87/399)	p<0.001
Safety[g]	n=404	n=399	
Patients reporting at least 1 adverse event	71.5% (289/404)	68.9% (275/399)	No statistical testing reported
Patients reporting at least 1 serious adverse event	5.0% (20/404)	5.0% (20/399)	No statistical testing reported
Patients reporting adverse events leading to discontinuation	3.0% (12/404)	4.0% (16/399)	No statistical testing reported
Patients experiencing any hypoglycaemia	4.5% (18/404)	1.5% (6/399)	No statistical testing reported

Notes: HbA1c conversions used the formula: IFCC HbA1c (mmol/mol)=[DCCT HbA1c (%)−2.15]×10.929

Abbreviations: Alo25, alogliptin 25 mg; CI, confidence interval; FPG, fasting plasma glucose; LS, least square; Met, metformin ≥1500 mg or maximum tolerated dose; NS, not statistically significant; Pio30, pioglitazone 30 mg; Pio45, pioglitazone 45 mg; SD, standard deviation; SE, standard error.

[a] All patients who were randomly assigned to receive double-blind study drug.

[b] Per-protocol population: all randomised participants who had received at least 1 dose of double-blind study drug, had a baseline and at least 1 post-baseline HbA1c measurement, and had no major protocol violations using last observation carried forward to account for missing data.

[c] Non-inferiority: non-inferiority was assessed using a planned interim analysis at 26 weeks and a final analysis at 52 weeks, using one-sided 97.5% confidence intervals for LS mean change in HbA1c from baseline. Non-inferiority was assessed using a margin of 0.3%.

[d] Superiority: superiority was assessed using a final analysis at 52 weeks, using one-sided 97.5% confidence intervals for LS mean change in HbA1c from baseline.

[e] Modified intention-to-treat population: all randomised participants who had received at least 1 dose of double-blind study drug and had a baseline and at least 1 post-baseline measurement using last observation carried forward to account for missing data.

[f] Rescue therapy for hyperglycaemia was initiated if FPG levels fell outside of pre-specified thresholds at different time points throughout the study.

[g] Modified intention-to-treat population: all randomised participants who had received at least 1 dose of study drug.

Table 3 Summary of primary outcomes from 4 placebo-controlled trials

Study	Least square mean change in HbA1c baseline to week 26: placebo	Least square mean change in HbA1c baseline to week 26: alogliptin	Absolute difference in least square mean change in HbA1c between placebo and alogliptin

Pratley et al. (2009a) (add on to pioglitazone)	−0.19% [−2.1 mmol/mol]	12.5 mg: −0.66% [−7.2 mmol/mol] 25 mg: −0.80% [−8.7 mmol/mol]	Difference: 0.47% [5.1 mmol/mol] Difference: 0.61% [6.7 mmol/mol] p<0.001 for both versus placebo
Pratley et al. (2009b) (add on to sulfonylurea)	+0.01% [+0.1 mmol/mol]	12.5 mg: −0.38% [−4.2 mmol/mol] 25 mg: −0.52% [−5.7 mmol/mol]	Difference: 0.39% [4.3 mmol/mol] Difference: 0.53% [5.8 mmol/mol] p<0.001 for both versus placebo
Rosenstock et al. (2009) (add on to insulin)	−0.13% [−1.4 mmol/mol]	12.5 mg: −0.63% [−6.9 mmol/mol] 25 mg: −0.71% [−7.8 mmol/mol]	Difference: 0.50% [5.5 mmol/mol] Difference: 0.58% [6.3 mmol/mol] p<0.001 for both versus placebo
DeFronzo et al. (2012) (add on to metformin and pioglitazone[a])	−0.9% [−9.8 mmol/mol]	12.5 mg: −1.4% [15.3 mmol/mol] 25 mg: −1.4% [15.3 mmol/mol]	Difference: 0.5% [5.5 mmol/mol] Difference: 0.5% [5.5 mmol/mol] p<0.001 for both versus placebo

Notes: HbA1c conversions used the formula: IFCC HbA1c (mmol/mol)=[DCCT HbA1c (%)−2.15]×10.929

[a] Results from different doses of pioglitazone (15mg, 30mg, 45 mg) combined

Concurrent treatments:

Pratley et al. (2009a): pioglitazone (metformin and sulfonylurea at pre-study enrolment doses permitted).

Pratley et al. (2009b): glyburide (a sulfonylurea).

Rosenstock et al. (2009): insulin with or without metformin.

DeFronzo et al. (2012): metformin; then randomised to placebo, alogliptin, pioglitazone, or alogliptin plus pioglitazone.

Clinical effectiveness

Alogliptin in dual therapy

Four key placebo-controlled, phase III, RCTs compared alogliptin add-on therapy (12.5 mg and 25 mg daily) with placebo in adults with type 2 diabetes and inadequate glycaemic control after taking metformin (Nauck et al. 2009), pioglitazone (some participants also received metformin or a sulfonylurea, Pratley et al. 2009a), a sulfonylurea (glyburide, Pratley et al. 2009b), or stable insulin therapy with or without metformin (Rosenstock et al. 2009).

All included 26-week treatment periods and all reported a primary outcome of least squares mean change in HbA1c from baseline to week 26. All 4 RCTs found that alogliptin add-on therapy (12.5 mg or 25 mg daily) led to statistically significantly greater improvements in HbA1c from baseline to week 26 compared with placebo, across the range of concurrent treatment classes. The absolute differences for this primary outcome for the 4 placebo-controlled RCTs are displayed in table 1 (Nauck et al. 2009) and table 3 (Pratley et al. 2009a, Pratley et al. 2009b and Rosenstock et al. 2009). Using alogliptin as an add-on therapy (12.5 mg or 25 mg daily) for a period of 26 weeks led to an additional reduction in HbA1c in the region of 5.5 mmol/mol (0.5 percentage points) compared with placebo across a range of concurrent treatment options.

Nauck et al. (2009) reported statistically significantly greater reductions in HbA1c at 26 weeks using dual therapy (alogliptin [12.5 mg or 25 mg daily] in combination with metformin [≥1500 mg or maximum tolerated dose daily]), compared with monotherapy (placebo in combination with metformin [≥1500 mg or maximum tolerated dose daily]). At week 26, the least squares mean change from baseline in HbA1c was −0.6% [−6.6 mmol/mol] for both alogliptin groups compared with −0.1% [−1.1 mmol/mol] for the placebo group (p<0.001; table 1).

The incidence of hyperglycaemic rescue with monotherapy (24%) was statistically significantly higher compared with dual therapy (9% with alogliptin 12.5 mg, p<0.004 and 8% with alogliptin 25 mg, p<0.003) at 26 weeks. Statistically significant improvements using dual therapy over monotherapy were also observed for the proportion of patients achieving HbA1c levels ≤7.0% [53 mmol/mol] and ≤6.5% [48 mmol/mol] and change from baseline in fasting blood glucose levels. No statistically significant differences were found for fasting proinsulin and insulin levels, homeostasis model of assessment of beta-cell function, or blood lipid variables. There was also no statistically significant difference in change from baseline in weight between the alogliptin groups and the placebo group (table 1).

Alogliptin in triple therapy

Bosi et al. (2011) reported statistically significantly greater reductions in HbA1c at 26 and 52 weeks (co-primary outcomes) using triple therapy (alogliptin [25 mg daily] in combination with metformin [≥1500 mg or maximum tolerated dose daily] and pioglitazone [30 mg daily]) compared with dual therapy (metformin [≥1500 mg or maximum tolerated dose daily] and pioglitazone [45 mg daily]). The least squares mean change from baseline in HbA1c using triple therapy was −0.89% [−9.7 mmol/mol] at 26 weeks and −0.70% [−7.7 mmol/mol] at 52 weeks compared with −0.42% [−4.6 mmol/mol] and −0.29% [-3.2 mmol/mol] respectively, using dual therapy (both p<0.001). The additional reductions in HbA1c with triple therapy were judged to be non-inferior at week 26 (LS mean difference −0.47%; 97.5% CI −∞ to −0.35%), and non-inferior and superior at week 52 (LS mean difference −0.42%; 97.5% CI −∞ to −0.28%), table 2).

Improvements in HbA1c peaked at around week 20 in both treatment groups. However, there was a trend toward an increase in HbA1c thereafter that had not levelled off by the end of the study (week 52).

The incidence of hyperglycaemic rescue using dual therapy (21.8%) was statistically significantly higher compared with triple therapy (10.9%, p<0.001) over the course of the study.

At week 52, statistically significant improvements using triple therapy over dual therapy were also observed for the proportions of patients achieving HbA1c levels ≤7.0% [53 mmol/mol] and ≤6.5% [48 mmol/mol], change from baseline in fasting blood glucose levels, fasting proinsulin/insulin ratio, and homeostasis model assessments of beta-cell function. No statistically significant differences were found for change in C-peptide, homeostasis model assessments of insulin resistance, or blood lipid and cholesterol parameters. Both treatment groups gained over a kilogram in weight but there was no statistically significant difference between the 2 groups (p=0.071, table 2).

DeFronzo et al. (2012) also reported statistically significantly greater improvements in HbA1c using triple therapy (alogliptin [12.5 mg or 25 mg daily] in combination with metformin [≥1500 mg daily] and pioglitazone [15 mg, 30 mg or 45 mg daily, results from different doses combined, hereafter referred to as 15/30/45 mg]) compared with dual therapy (metformin [≥1500 mg daily] and pioglitazone [15/30/45 mg daily]) after 26 weeks of treatment.

The least squares mean change from baseline in HbA1c using 12.5 mg or 25 mg alogliptin triple therapy was −1.4% (−15.3 mmol/mol) at week 26 compared with −0.9% (−9.8 mmol/mol) using dual therapy, an absolute difference of 0.5% (5.5 mmol/mol) (p<0.001, table 3).

Safety

No statistical testing was undertaken for differences in safety outcomes in either of the 2 main RCTs (Bosi et al. 2011 and Nauck et al. 2009).

Nauck et al. (2009) reported that the proportion of patients experiencing at least 1 adverse event was similar across each treatment group (Met+Placebo: 66%, Met+Alo12.5: 63% and Met+Alo25: 57%). Most adverse events were reported to be of mild intensity and considered by the investigator to be unrelated to the study drug. The proportion of patients experiencing serious adverse events, adverse events leading to study drug discontinuation, or hypoglycaemia was low across all groups (table 1).

Bosi et al. (2011) reported that 71.5% of patients receiving alogliptin triple therapy (Met+Pio30+Alo25) experienced a treatment-emergent adverse event, compared with 68.9% of patients receiving dual therapy (Met+Pio45). The most common adverse events in patients receiving alogliptin triple therapy over the 52-week study were upper respiratory tract infection (7.2%, 29/404), nasopharyngitis (6.9%, 28/404), hypertension (5.9%, 24/404) and urinary tract infection (5.4%, 22/404).

A total of 21.8% of patients (88/404) receiving alogliptin triple therapy in the study by Bosi et al. (2011) experienced drug-related adverse events compared with 18.8% (75/399) on dual therapy. The majority of adverse events were reported to be rated as mild or moderate in intensity.

The proportions of patients experiencing adverse events leading to study drug discontinuation (3.0%, 12/404) or serious adverse events (5.0%, 20/404) while using triple therapy were numerically similar to those on dual therapy (table 2). The study reports that a higher proportion of patients using triple therapy (5.2%, 21/404) compared with dual therapy (2.3%, 9/399) experienced drug-related skin and subcutaneous disorders, most commonly pruritus and rash (statistical

significance not reported). Hypoglycaemia was also reported by proportionally more patients on triple therapy (4.5%, 18/404, 2 cases were severe) compared with dual therapy (1.5%, 6/399), but again statistical significance was not reported.

Evidence strengths and limitations

The 2 RCTs had acceptable sample sizes for the end points they were considering (see tables 1 and 2) and were well designed, so their findings can be considered broadly reliable. However, they both have important limitations to consider.

The evidence presented in this evidence summary relates to a maximum follow-up period of 52 weeks and so the long-term efficacy and safety of alogliptin is not known. The RCTs reviewed demonstrated the efficacy of alogliptin with regard to surrogate outcomes related to HbA1c. As is usual at this stage of development of a blood glucose-lowering drug, there are no data for the effect of alogliptin on the long-term complications of type 2 diabetes that are of direct importance to patients, such as rates of macrovascular or microvascular events. However, longer-term studies (ENDURE and EXAMINE) are ongoing and a pooled analysis of phase II and III RCTs of alogliptin has recently been published (White et al. 2013).

The studies reviewed in this evidence summary focus on adding alogliptin to metformin, or metformin and pioglitazone, in adults with type 2 diabetes who had inadequate glycaemic control. The efficacy of alogliptin in the context of other possible dual or triple therapies has been explored in other studies not reviewed in detail here (as add-on therapy to pioglitazone, a sulfonylurea or insulin [with or without metformin], see table 3). However, no studies are available in which alogliptin has been added to metformin and a sulfonylurea, or in which alogliptin has been compared with other DPP-4 inhibitors or glucagon-like peptide-1 (GLP-1) mimetics (Takeda UK Ltd: personal communication April 2013).

Both Bosi et al. (2011) and Nauck et al. (2009) had run-in periods before randomisation, in which 13% and 12%, respectively, of eligible participants were excluded. Both trials also used last observation carried forward in their analysis to account for missing data. Study completion rates in Nauck et al. (2009) were 69.2% (Met+placebo), 82.6% (Met+Alo12.5) and 78.6% (Met+Alo25). In Bosi et al. (2011) they were 70.0% (Met+Pio30+Alo25) and 60.9% (Met+Pio45).

The primary analysis in Bosi et al. (2011), a non-inferiority and superiority trial, used a per-protocol data set that can introduce bias. This excluded 25% of those initially randomised (101/404) into the alogliptin triple therapy group, and 23% of the dual therapy group (93/399). The authors reported that similar results were obtained when the intention-to-treat data set was used, but figures for

this were not reported. Treatment allocation concealment was also not described in this study and is an additional potential source of bias.

It is worth noting that Bosi et al. (2011) reported that improvements in HbA1c peaked at around week 20 (in both triple and dual therapy groups) and there was a trend toward an increase in HbA1c thereafter that had not levelled off at the end of the study (week 52). Studies recording HbA1c past 1 year would be needed to assess whether the beneficial effect of alogliptin further diminishes over time.

Context

Treatment alternatives

The currently licensed dipeptidyl peptidase-4 (DPP-4) inhibitors are:

- Sitagliptin

- Vildagliptin

- Saxagliptin

- Linagliptin.

The introduction gives details of current NICE recommendations for DPP-4 inhibitors. See the relevant summary of product characteristics for licensed indications.

Other blood glucose-lowering drug therapies for treating type 2 diabetes include metformin, sulfonylureas, pioglitazone, GLP-1 mimetics (exenatide, liraglutide and lixisenatide), and insulin.

Costs of treatment alternatives

Drug	Usual dosage[a]	28-day costs excluding VAT[b]
Sitagliptin	100 mg once daily	£33.26
Vildagliptin	50 mg twice daily	£31.76
Saxagliptin	5 mg once daily	£31.60
Linagliptin	5 mg once daily	£33.26

Estimated impact for the NHS

Likely place in therapy

The 2 RCTs reviewed in this evidence summary used alogliptin in combination with metformin (dual therapy), or alogliptin in combination with metformin and pioglitazone (triple therapy). Alogliptin has also been investigated as dual therapy, added to pioglitazone, a sulfonylurea or insulin (with or without metformin).

Usual clinical practice, based on the NICE clinical guideline on type 2 diabetes, would be to add a sulfonylurea to metformin unless contraindicated or not tolerated, followed by the addition of insulin or another blood glucose-lowering drug if glycaemic control remains inadequate.

As outlined in the introduction, current NICE guidance recommends DPP-4 inhibitors as a second-line treatment option in combination with metformin or a sulfonylurea (after first-line metformin or sulfonylurea monotherapy) and as a third-line treatment option (after first-line metformin and a second-line sulfonylurea), in line with the licensed indications of the DPP-4 inhibitors available at the time of publication. Further guidance on the place in therapy of the 4 DPP-4 inhibitors currently available (sitagliptin, vildagliptin, saxagliptin and linagliptin), but not alogliptin, will be given in the update of the NICE clinical guideline on type 2 diabetes.

Adding a new drug, such as alogliptin, to metformin monotherapy (Nauck et al. 2009) or sulfonylurea monotherapy (Pratley et al. 2009b) could be considered to fall within usual clinical practice if adding a sulfonylurea or metformin is not appropriate. However, adding such a new drug to pioglitazone (Pratley et al. 2009a) or insulin (Rosenstock et al. 2009) would be a less common approach, reducing the relevance of these trials to UK practice. Likewise, adding a new drug, such as alogliptin, to metformin plus pioglitazone (Bosi et al. 2011) would not be common UK practice. To help local decision makers have a clearer understanding of the drug's place in therapy, a study investigating alogliptin added to metformin plus a sulfonylurea , and further active comparator studies comparing alogliptin with other DPP-4 inhibitors or glucagon-like peptide-1 (GLP-1) mimetics would be useful.

The proposed marketing authorisation for alogliptin indicates that it will be licensed for use in combination with other glucose-lowering medicinal products including insulin. The typical

proposed dose for alogliptin is 25 mg taken once daily as an oral tablet. A reduced dose is advised for people with moderate or severe renal impairment, or end-stage renal disease (Takeda UK Ltd: personal communication February 2013). The NHS list price for alogliptin is not yet known. The 28-day drug cost for usual doses of the DPP-4 inhibitors currently available ranges from £31.60 to £33.26 (see Costs of treatment alternatives).

Local decision makers will need to consider the available evidence on efficacy and safety, as well as cost and individual patient factors, when making decisions about using alogliptin.

Estimated usage

It is not possible to provide estimated usage based on the available data. The manufacturer estimates an uptake of 5%, 10% and 15% of the eligible population in years 1, 3 and 5 respectively, within the DPP-4 inhibitor class (Takeda UK Ltd: personal communication February 2013).

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Changes after publication

October 2014:

Update

The following information has become available since this ESNM was produced.

January 2014: Availability of alogliptin

Alogliptin has been launched in the UK as Vipidia (alogliptin benzoate) and Vipdomet (metformin hydrochloride plus alogliptin benzoate). The cost of Vipidia (excluding VAT, all strengths) is £26.60 for 28 tablets. The cost of Vipdomet (excluding VAT) is £26.60 for 56 tablets. Costs taken from MIMS, September 2014.

October 2013: Study finds no benefit from alogliptin on cardiovascular outcomes in people with a recent acute coronary syndrome

A large randomised controlled trial (EXAMINE) has found that adding alogliptin to other blood-glucose-lowering medication did not reduce the risk of cardiovascular events in people with type 2 diabetes who had had a recent acute coronary syndrome, over a median of 18 months. This study was summarised in a medicines evidence commentary.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

For information about the process used to develop this evidence summary, see Evidence summaries: new medicines – interim process statement.

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