NHS
Vale of York
Clinical Commissioning Group

COMMISSIONING POLICY RECOMMENDATION
TREATMENT ADVISORY GROUP
Policy agreed by (*Vale of York CCG/date*)

Drug, Treatment, Device name		
Alogliptin (Vipidia; Takeda)		
Licensed indication		
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.		
Cost per patient (at recommended dose)		
Alogliptin tablets	25mg daily	£26.60
Sitagliptin	100mg daily	£33.26
Vildagliptin	50mg BD	£31.76
Saxagliptin	5mg OD	£31.60
Linagliptin	5mg OD	£33.26
Resource impact on population		
As this drug will just be another treatment option as set out in the present NICE clinical guideline for Diabetes. It is unlikely to result in any significant resource impact for CCGs.		
Recommendation to Routinely Commission **OR** **Not Routinely Commission** **OR** **Commission under criteria**		
When is funding appropriate?		
Alogliptin is not recommended for treatment of type 2 diabetes due to the lack of clinical advantages over other DPP-4 inhibitors that are already used in clinical practice. CCGs may wish to consider the cost savings if alogliptin was approved although need to take into account that sitagliptin will be the first to come off patent in 2022.		
Clinical and cost effectiveness evidence		
NICE Clinical Guideline 87: Type 2 Diabetes May 2009 **http://publications.nice.org.uk/type-2-diabetes-cg87** This clinical guideline is currently being updated, but the marketing authorisation for alogliptin is not anticipated in time for inclusion within the guideline. The guidance does however, state the following: • 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%, 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%, or other higher level agreed with the individual) if:
- the person does not tolerate metformin, or metformin is contraindicated.
• Consider adding sitagliptin 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% or other higher level agreed with the individual) and insulin is unacceptable or inappropriate.
• 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 in HbA1c in 6 months).
• 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, rosiglitazone) 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 used on patient preference.

NICE clinical pathway: Diabetes
http://pathways.nice.org.uk/pathways/diabetes

NICE Evidence summary ESNM20: Type 2 diabetes – alogliptin.
http://publications.nice.org.uk/esnm20-type-2-diabetes-alogliptin-esnm20

Clinical Evidence

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 multicenter, randomized, double-blind, placebo-controlled study.
Nauck et al.
Int J Clin Pract January 2009, 63,1, 46-55.

The aim of this study was to evaluate the efficacy and safety of alogliptin, for 26 weeks at once daily doses of 12.5mg and 25mg in combination with metformin in patients whose HbA1c levels were inadequately controlled on metformin alone.
This was a 26 week, randomized double blind, placebo controlled clinical trial. Study patients had a history of type 2 diabetes and inadequate glycaemic control (HbA1c between 7%-10%) despite being on metformin monotherapy for at least 3 months. Other inclusion criteria included nBMI between 23-45kg/m^2. Exclusion criteria included laser treatment for DMO within 6 months, new york heart association class III or IV heart failure, or history of coronary angioplasty, coronary bypass surgery, coronary stent placement or MI within last 6 months.

Patients were randomized to continue to take stable metformin dose regimen plus the addition of either placebo (n=104) or alogliptin at once daily dose of 12.5mg (n=213) or 25mg (n=210). At baseline mean HbA1c was 7.9%-8%, mean BMI was 32kg/m^2, mean duration of diagnosed diabetes was 6 years and mean metformin dose was 1847mg per day.
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 , fasting C-peptide, body weight and clinical response as measured by the incidence of HbA1c decrease from baseline of at least 0.5% or at least 1% at week 26.
Alogliptin at either dose produced least squares mean decreases from baseline in HbA1c of -0.6% vs -0.1% for placebo (p<0.01).
LS mean change in FPG from baseline to week 26 was -1mmol/l for both strengths vs 0mmol/l for placebo (p<0.001 for both). Patients achieving HbA1c ≤7% at week 26 was 52% (12.5mg alogliptin group, 44% (25mg alogliptin group) vs 18% in the placebo group. The LS mean difference in body weight versus placebo was 0kg in the 12.,5mg group and -0.3kg in the 25mg group. Overall, adverse events observed with alogliptin were not substantially from those observed with placebo.

Alogliptin as a third oral antidaibetic 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.
Bosi et al
Diabetes Obes Metab. 2011 Dec; 13(12): 1088-96

This study was to assess the efficacy and safety of adding alogliptin versus uptitrating pioglitazone in patients with type 2 diebetes and inadequate glycaemic control on metformin and pioglitazone.
This was a randomized, double blind, active controlled, parallel-group study, patients with type 2 diabetes and a HbA1c ≥7% and ≤10% on metformin (≥1500mg or maximum tolerated dose) and pioglitazone 30mg received alogliptin 25mg (404 patients) or pioglitazone 15mg (399 patients) added to Metformin+pioglitazone 30mg for 52 weeks. The primary endpoint was change from baseline in HbA1c at weeks 26 and 52, with sequential testing for non-inferiority of Metformin+Pioglitazone 30mg+ alogliptin 25mg at weeks 26 and 52 and then for superiority at week 52.
Met+Pio30+Alo25 showed superior glycaemic control versus Met+Pio45 at week 52 [least squares (LS) mean CFB in A1c, -0.70 vs. -0.29%; p < 0.001]. At week 52, Met+Pio30+Alo25 resulted in greater CFB in A1c regardless of baseline A1c (p < 0.001); higher proportions of patients achieving A1c ≤7.0 (33.2 vs. 21.3%) and ≤6.5% (8.7 vs. 4.3%; p < 0.001); greater CFB in fasting plasma glucose (FPG; LS mean CFB, -0.8 vs. -0.2 mmol/L; p < 0.001); and greater improvements in measures of β-cell function (p < 0.001). Hypoglycaemia incidence was low (Met+Pio30+Alo25, 4.5%; Met+Pio45, 1.5%), mostly mild to moderate, but with two severe events in the Met+Pio30+Alo25 group. No meaningful differences in incidences of individual adverse events were observed between treatments.

Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin added to pioglitazone in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study.

Pratley RE et al.
Curr Med Res opin 2009 Oct;25: 2361-71

This was a multicenter, double-blind, placebo- controlled clinical trial, 493 patients with inadequate glycemic control (HbA1c 7-10%) despite treatment with pioglitazone were randomly assigned to treatment with pioglitazone with alogliptin 12.5mg, alogliptin 25mg or placebo. Concomitant therapy with metformin or sulfonurea at prestudy doses was permitted.
The primary endpoint was change in hbA1c from baseline to week 26. . Secondary endpoints included changes in fasting plasma glucose (FPG) and body weight, and incidences of marked hyperglycemia (FPG > or = 200 mg/dL [11.10 mmol/L]) and rescue for hyperglycemia.
Least squares (LS) mean change in HbA(1c) was significantly ($p < 0.001$) greater for alogliptin 12.5 mg (-0.66%) or 25 mg (-0.80%) than for placebo (-0.19%). A significantly ($p <$ or = 0.016) larger proportion of patients achieved HbA(1c) < or = 7% with alogliptin 12.5 mg (44.2%) or 25 mg (49.2%) than with placebo (34.0%). LS mean decreases in FPG were significantly ($p = 0.003$) greater with alogliptin 12.5 mg (-19.7 mg/dL [-1.09 mmol/L]) or 25 mg (-19.9 mg/dL [-1.10 mmol/L]) than with placebo (-5.7 mg/dL [-0.32 mmol/L]). The percentage of patients with marked hyperglycemia was significantly ($p < 0.001$) lower for alogliptin (< or =25.0%) than placebo (44.3%). The incidences of overall adverse events and hypoglycemia were similar across treatment groups, but cardiac events occurred more often with active treatment than placebo.

Alogliptin added to insulin therapy in patients with type 2 diabetes reduces HbA(1C) without causing weight gain or increased hypoglycaemia.
Rosenstock j et al
Diabetes Obes. Metab. 2009 Dec; 11(12): 1145-52

In this 26-week, double-blind, placebo-controlled study, 390 patients were randomized to receive alogliptin 12.5 mg (n = 131), alogliptin 25 mg (n = 129) or placebo (n = 130) once daily, as add-on to stable insulin therapy with or without metformin. The primary endpoint was change in haemoglobin A(1C) (HbA(1C)) at week 26.
At week 26, mean HbA(1C) changes from the mean baseline value of 9.3% were significantly greater for alogliptin 12.5 mg (-0.63 +/- 0.08%) and alogliptin 25 mg (-0.71 +/- 0.08%) than placebo (-0.13 +/- 0.08%; $p < 0.001$). Significantly greater proportions of patients receiving alogliptin 12.5 or 25 mg than placebo had HbA(1C) decreases of > or =0.5, > or =1.0 and > or =1.5%. Insulin doses remained unchanged, and there were no differences in the proportions of patients experiencing hypoglycaemia among placebo (24%), alogliptin 12.5 mg (27%) and alogliptin 25 mg (27%). Mean weight increases from baseline at week 26 were similar for placebo (0.6 +/- 0.2 kg), alogliptin 12.5 mg (0.7 +/- 0.2 kg) and alogliptin 25 mg (0.6 +/- 0.2 kg). Incidences of overall adverse events, and of gastrointestinal, dermatological and infection-related events, were similar among groups.

Points for consideration

- Alogliptin is a new oral selective inhibitor of dipeptidyl peptidase-4 (DPP-4) which is licensed to improve glycaemic control in adults aged 18 yrs and older with type 2 diabetes in combination with other glucose-lowering medicinal products including

insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

- This will be another option compared to sitagliptin, vildagliptin, saxagliptin and linagliptin.
- NICE clinical guideline for diabetes advises on the place in therapy for DPP-4 inhibitors.
- Alogliptin as add-on therapy reduces HbA1c by around 5.5mmol/mol (0.5%) compared with placebo in both dual and triple therapy.
- There are no published RCTs of alogliptin added to metformin and a sulfonurea, or alogliptin compared with other DPP-4 inhibitors or GLP-1 mimetics.
- There is a requirement to make a dose reduction in patients with renal impairment.
- Since there is limited experience of alogliptin use in clinical trials in patients with congestive heart failure of New York Heart Association (NYHA) functional class III - IV use should not be recommended in these patients.
- There does not appear to be any significant clinical advantages over other DPP-4 inhibitors but overall this is the cheapest treatment option available at present. Consideration that Sitagliptin will come off patent first in 2022 (as well as vildagliptin) although others are not known yet.
- The SPC has the following warnings:
    - Due to the increased risk of hypoglycaemia in combination with a sulphonylurea, insulin or combination therapy with thiazolidinedione plus metformin, a lower dose of these medications may be considered to reduce the risk of hypoglycaemia when these medicinal products are used in combination with alogliptin.
    - Alogliptin has not been studied in combination with sodium glucose cotransporter 2 (SGLT-2) inhibitors or glucagon like peptide 1 (GLP-1) analogues and as triple therapy with metformin and a sulphonylurea.

Health gains

Clinical benefits gained from this treatment are disease orientated outcomes as reported in clinical trials, reduction In HbA1c and mean fasting plasma glucose. There is an absence of clinical evidence to support patient orientated outcomes e.g. mortality.

Patient safety / pharmacovigilance

The most common adverse effects are upper respiratory infections, Nasopharyngitis, headache, abdominal pain, Gastroesophageal reflux disease, pruritis and rash.

When to stop treatment

Reduction in HbA1c of less than 0.5% after 6 months.

Who prescribes?

Alogliptin may be prescribed by GPs and other non medical prescribers, following initiation and or recommendation from a clinician specialising in diabetes

Stakeholder views	
Equity of access	
SPECIFICATION DATE, REVIEW DATE, AND LEAD NAME/JOB TITLE	
Origin Date: January 2014	Originator:Christopher Ranson
TAG Review Date:	
TAG Recommendation Date:	

Impact on individual clinical commissioning groups								
12 months Rx (Dec'12-Nov ,13)	**Sitagliptin**	**12 month Saving if equiv Alogliptin Prescribed**	**Linagliptin**	**12 month Saving if equiv Alogliptin Prescribed**	**Saxagliptin**	**12 month Saving if equiv Alogliptin Prescribed**	**Vildagliptin**	**12 month Saving if equiv Alogliptin Prescribed**
AWC CCG	£186,187.34	£40,361.03	£7,216.38	£1,563.44	£7,208.56	£409.61	£2,714.95	£138.75
EAST RIDING CCG	£315,372.09	£68,375.84	£71,503.78	£15,501.15	£57,936.52	£3,294.21	£40,742.64	£2,077.53
HamRichWhitby	£132,366.73	£28,701.51	£38,108.10	£8,263.40	£8,448.10	£480.57	£2,619.32	£133.88
HaRD	£132,715.29	£28,778.81	£33,763.69	£7,320.05	£3,092.95	£175.96	£5,718.11	£292.50
HULL CCG	£311,640.44	£67,538.58	£12,263.69	£2,657.34	£119,949.68	£6,815.90	£11,256.18	£575.14
NE LINCS CCG	£207,235.12	£44,901.01	£16,455.43	£3,563.81	£22,601.95	£1,285.26	£3,616.18	£184.71
NORTH LINCS CCG	£237,061.73	£51,395.70	£34,562.26	£7,489.65	£34,562.26	£1,049.12	£13,568.58	£693.38
Scar Rye	£135,897.37	£29,459.08	£31,215.84	£6,765.13	£3,093.27	£175.96	£7,347.46	£375.75
VoY CCG	£364,575.86	£79,052.06	£57,008.54	£12,350.97	£33,325.11	£1,895.31	£13,484.37	£689.25