Arden&GEM

NHS
Arden and Greater East Midlands Commissioning Support Unit

Arden and Greater East Midlands Commissioning Support Unit in association with Lincolnshire Clinical Commissioning Groups, Lincolnshire Community Health Services, United Lincolnshire Hospitals Trust and Lincolnshire Partnership Foundation Trust

Lincolnshire Prescribing and Clinical Effectiveness Bulletin

Volume 10; Number 12 **August 2016**

REVIEW OF DIPEPTIDYL PEPTIDASE 4 INHIBITORS (OR GLIPTINS) IN DIABETES

- **Alogliptin (*Vipidia*) is non-inferior to other DPP-4 inhibitors and significantly lower in cost than competitors. It is now the preferred first line DPP-4 inhibitor on the *Lincolnshire Joint Formulary* and should be prescribed preferentially in new patients requiring a DPP-4 inhibitor. Even in patients with renal impairment, alogliptin can usually be prescribed, subject to recommended dosage adjustments, although it should be avoided in severe renal impairment. Designation: GREEN first line.**
- **Existing patients on alternative DPP-4 inhibitors should be reviewed and considered for a therapeutic switch to alogliptin.**
- **Sitagliptin (*Januvia*) is no longer recommended as the first line DPP-4 inhibitor of choice, although it can be considered as a second line alternative to alogliptin. Designation: GREEN second line.**
- **Linagliptin (*Trajenta*) requires no dosage adjustment in renal and hepatic impairment and can be considered as a second line alternative to alogliptin in those with severe renal impairment or hepatic impairment. Designation: GREEN second line (see page).**
- **In view of declining use, saxagliptin (*Onglyza*) has been removed from the *Lincolnshire Joint Formulary.* Designation: RED-RED.**
- **Vildagliptin (*Galvus*) is not approved for use through the *Formulary* and remains RED-RED.**
- **The American Food and Drug Administration (FDA) recently published a safety review of saxagliptin and alogliptin that identified a possible increased risk of hospitalisation for heart failure in patients taking these medicines who already have heart or kidney disease. As a result of this, additional warnings and precautions have been added to the labels of both these products in the USA. PACEF have reviewed the trial evidence linking both drugs to increased hospitalisation due to heart failure and acknowledge that there is a small increased risk, particularly in those with pre-existing heart or kidney disease. At this stage, it is too early to tell whether this is potentially a risk with all DPP-4 inhibitors or whether this is related solely to specific agents.**
- **When initiating new patients on alogliptin or switching existing patients to alogliptin, prescribers should be mindful of existing SPC advice which is to avoid in severe renal impairment and exercise caution in those with pre-existing heart failure. All patients taking alogliptin or saxagliptin (or any other DPP-4 inhibitor) should be advised to contact their healthcare professional right away if they develop the signs and symptoms of heart failure such as unusual shortness of breath during daily activities, breathing difficulties when lying down, tiredness, weakness, fatigue or weight gain with swelling of the ankles, feet, legs or stomach. The MHRA have not yet published on this issue, but may choose to do so imminently. Local guidance and switch protocols will be amended in accordance with any subsequent advice from the MHRA.**

SUMMARY OF PACEF DECISIONS: *JUNE 2016 UPDATE*

Device, Dressing or Drug	**Indication(s)**	**Traffic Light and *Joint Formulary* Status**
Alogliptin 6.25mg, 12.5mg and 25mg tablets (*Vipidia*)	For the management of type 2 diabetes mellitus in adults to improve glycaemic control in combination with other glucose lowering therapies, including insulin when these together with diet and exercise do not provide adequate glycaemic control.	GREEN First line DPP-4 inhibitor of choice. Included in the *Lincolnshire Joint Formulary.*
Alogliptin/metformin 12.5mg/1g tablets (*Vipdomet*)	For the management of type 2 diabetes mellitus in adults: - as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of alogliptin and metformin. - in combination with pioglitazone (i.e. triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and pioglitazone. - in combination with insulin (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control.	GREEN Alogliptin is the first line DPP-4 inhibitor of choice. Included in the *Lincolnshire Joint Formulary.*
Linagliptin 5mg tablets (*Trajenta*) (Boehringer Ingelheim)	For the treatment of type 2 diabetes inadequately controlled by diet and exercise; as monotherapy when metformin is inappropriate ; with metformin when metformin alone is inadequate; with metformin and a sulfonylurea when dual therapy is inadequate ; or with insulin when insulin, with or without metformin , is inadequate.	GREEN Second line DPP-4 inhibitor approved for use in patients with severe renal or hepatic impairment. Included in the *Lincolnshire Joint Formulary.*
Linagliptin/metformin 2.5mg/850mg and 2.5mg/1g (*Jentadueto*) (Boehringer Ingelheim)	For the treatment of type 2 diabetes inadequately controlled by diet and exercise; when metformin alone is inadequate; in patients who are currently receiving the combination as separate tablets; with a sulfonylurea when a sulfonylurea plus metformin is inadequate; or with insulin when insulin plus metformin is inadequate.	GREEN Linagliptin is a second line DPP-4 inhibitor approved for use in patients with severe renal or hepatic impairment. Included in the *Lincolnshire Joint Formulary.*
Saxagliptin 2.5mg and 5mg tablets (*Onglyza*) (AstraZeneca)	For the treatment of type 2 diabetes inadequately controlled by diet and exercise; as monotherapy when metformin is inappropriate; with metformin or a glitazone when either agent alone is inadequate; with a sulfonylurea when metformin is inappropriate and a sulfonylurea alone is inadequate; with metformin and a sulfonylurea when dual	RED-RED In view of continuing cardiovascular concerns and declining use, removed from the *Lincolnshire Joint Formulary.*

	therapy is inadequate or with insulin when insulin, with or without metformin, is inadequate.	
Saxagliptin/metformin 2.5mg/850mg and 2.5mg/1g tablets (*Komboglyza*) (AstraZeneca)	For the treatment of type 2 diabetes inadequately controlled by diet and exercise; when metformin alone is inadequate; in patients who are currently receiving the combination as separate tablets; with a sulfonylurea when a sulfonylurea plus metformin is inadequate; or with insulin when insulin plus metformin is inadequate.	RED-RED In view of continuing cardiovascular concerns and declining use, not approved for use on the *Lincolnshire Joint Formulary.*
Sitagliptin 100mg tablets (*Januvia*) (MSD)	Treatment of type 2 diabetes as monotherapy when metformin is inappropriate due to contraindications or intolerance, dual therapy in combination with metformin, sulfonlyurea or glitazone or triple oral therapy in combination with a sulfonylurea plus metformin or glitazone plus metformin or with insulin with or without metformin.	GREEN Second line DPP-4 inhibitor of choice. Included in the *Lincolnshire Joint Formulary.*
Sitagliptin 50mg/metformin 1g (*Janumet*) (MSD)	Treatment of type 2 diabetes as monotherapy when metformin is inappropriate due to contraindications or intolerance, dual therapy in combination with metformin, sulfonlyurea or glitazone or triple oral therapy in combination with a sulphonylurea plus metformin or glitazone plus metformin or with insulin with or without metformin.	GREEN Second line DPP-4 inhibitor/ metformin combination product of choice. Included in the *Lincolnshire Joint Formulary.*
Vildagliptin 50mg tablets (*Galvus*) (Novartis)	For the treatment of type 2 diabetes inadequately controlled by diet and exercise; as monotherapy when metformin is inappropriate; with metformin or a glitazone when either agent alone is inadequate; with a sulfonylurea when metformin is inappropriate and a sulfonylurea alone is inadequate; with metformin and a sulfonylurea when dual therapy is inadequate or with insulin when insulin, with or without metformin, is inadequate.	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*
Vildagliptin/metformin 50mg/850mg and 50mg/1g tablets (*Eucreas*) (Novartis)	For the treatment of type 2 diabetes inadequately controlled by diet and exercise; when metformin alone is inadequate; in patients who are currently receiving the combination as separate tablets; with a sulfonylurea when a sulfonylurea plus metformin is inadequate; or with insulin when insulin plus metformin is inadequate.	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*

This *Bulletin* has been created specifically to convey details of decisions taken at the Prescribing and Clinical Effectiveness Forum (PACEF) to all stakeholders across the Lincolnshire Healthcare Community in both primary and secondary care. Back issues of the *PACE Bulletin* and other PACEF publications are available through the PACEF website (http://lincolnshire-pacef.nhs.uk). Electronic copies of the *PACE Bulletin* are circulated to a wide readership via email. If you are not currently on our distribution list and wish to receive regular copies of PACEF publications please contact Sandra France on sandra.france@gemcsu.nhs.uk.

Google searching can be a quick and effective way of finding back numbers of the *PACE Bulletin* relevant to a specific topic of interest. Searchers are advised to use the official version of the *Bulletin* available from the PACEF website rather than depend on a potentially unreliable draft or variant found through Google or an alternative search engine.
The *Lincolnshire Joint Formulary* is available on line and is fully searchable; it can be accessed at www.lincolnshirejointformulary.nhs.uk

RED-RED: This signifies that a product is **not recommended** for prescribing in **either** primary or secondary care. All new products are classified as RED-RED pending assessment by PACEF.
RED: This signifies that a product has been approved for use within secondary care, tertiary care or a primary care hosted specialist service only and **should not be routinely prescribed in primary care**. RED drugs may be used within ULHT or LPFT subject to approval for use within each Trust. ULHT and LPFT reserve the right to determine whether or not RED drugs

will be used within their Trusts. RED classification does not automatically signify that a drug will be available within secondary/tertiary care.
AMBER: This signifies that a drug has been approved for use in primary care **subject to specialist initiation; a shared care guideline (SCG) may also be required**. The main purpose of the SCG will be to clearly define both specialist and GP responsibilities. Not all AMBER drugs that require SCGs are currently covered by formal documents; PACEF are working to rectify this.
GREEN: This signifies a product that is **approved for initiation in either primary or secondary care.**

REVIEW OF DIPEPTIDYL PEPTIDASE 4 INHIBITORS (OR GLIPTINS) IN DIABETES

Introduction

In recently published and updated NICE Guidelines on the management of type 2 diabetes in adults (NG28 (December 2015)), NICE make a number of key recommendations around appropriate treatment:

- Standard release metformin remains the first-line drug of choice for the initial management of adults with type 2 diabetes mellitus (DM).
- In adults with type 2 DM, if initial treatment with metformin has not continued to control HbA1c (defined as the persons individually agreed threshold for intensification), consider dual therapy with **either:** metformin and a DPP-4 inhibitor **or** metformin and pioglitazone **or** metformin and a sulfonylurea.
- In adults with type 2 DM, if metformin is contra-indicated or not tolerated and initial drug treatment has not continued to control HbA1c to below the person's individually agreed threshold for intensification consider dual therapy with **either:** a DPP-4 inhibitor and pioglitazone **or** a DPP-4 inhibitor and a sulfonylurea **or** pioglitazone and a sulfonylurea.
- In adults with type 2 DM, if dual therapy with metformin and another oral drug has not continued to control HbA1c consider **either:** triple therapy with metformin/DPP-4 inhibitor and sulfonylurea or metformin/pioglitazone and sulfonylurea or starting insulin-based treatment.
- If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide -1 (GLP-1) mimetic.

In an environment in which, prescribers are becoming increasingly cautious around the use of antidiabetic agents that can cause hypoglycaemia (see below) and pioglitazone is seen as having a limited role, DPP-4 inhibitors (or gliptins) are becoming increasingly widely prescribed.

Anti-diabetic drugs associated with hypoglycaemia
Insulins, sulfonylureas, meglitinides (nateglinide and repaglinide), sodium glucose co-transporter 2 inhibitors (canagliflozin, dapagliflozin and empagliflozin), pioglitazone and glucagon-like peptide-1 receptor agonists (exenatide, liraglutide, lixisenatide and dulaglutide).

The cost comparison below illustrates the disparity in price between conventional low cost first and second line agents, like metformin, sulfonylureas and pioglitazone, and the newer class of DPP-4 inhibitors. All four Lincolnshire CCGs are currently experiencing significant growth in diabetes prescribing costs and increasing second line use of DPP-4 inhibitors is a key contributor to this.

Drug	Dose	Cost (28 days)
Metformin		
Metformin 500mg tablets	500mg three times daily	£4.02
Metformin 850mg tablets	850mg twice daily	£1.94
Metformin 500mg modified release tablets	500mg daily	£2.66
Metformin 750mg MR tablets	750mg once daily	£3.20
Metformin 1g MR tablets	1g once daily	£4.26
Metformin 1g MR tablets	2g once daily	£8.52
Sulfonylurea		
Gliclazide 40mg tablets (generic)	40mg once daily	£3.36
Gliclazide 80mg tablets (generic)	80mg once daily	£1.13
Gliclazide 30mg modified release tablets	30mg once daily	£2.06
Gliclazide 60mg modified release tablets	60mg once daily	£4.77
Pioglitazone		
Pioglitazone 15mg tablets (generic)	15mg once daily	£1.19
Pioglitazone 30mg tablets	30mg once daily	£1.40
Pioglitazone 45mg tablets	45mg once daily	£1.60
DPP-4 inhibitors		
Alogliptin 25mg tablets (Vipidia) (Takeda UK Ltd)	25mg once daily	£26.60
Linagliptin 5mg tablets (Trajenta) (Boerhinger Ingelheim Ltd)	5mg once daily	£33.26
Saxagliptin 5mg tablets (Onglyza) (AstraZeneca UK Ltd)	5mg once daily	£31.60
Sitagliptin 100mg tablets (Januvia) (Merck Sharp and Dohme Ltd)	100mg once daily	£33.26
Vildagliptin 50mg tablets (Galvus) (Novartis Pharmaceuticals UK Ltd)	50mg twice daily	£33.35

In terms of treatment selection from within a therapeutic class, NICE have specifically stated that where 'two drugs in the same class are appropriate, choose the option with the lowest acquisition cost."

On the basis of this, PACEF has revisited a previous assessment of alogliptin (*Vipidia*) and alogliptin/metformin (*Vipdomet*) originally published in *PACE Bulletin* Volume 8 No 10 (May 2014). The cost comparison above illustrates that alogliptin is significantly lower in cost that alternative DPP-4 inhibitors. PACEF considered the proposal that: (1) alogliptin should become the first line DPP-4 inhibitor of choice on the *Lincolnshire Joint Formulary* and (2) that prescribers should consider switching existing patients on alternative DPP-4 inhibitors to alogliptin. As this review was underway, the American Food and Drink Administration published their safety review of alogliptin and saxagliptin emphasizing the possible increased risk of hospitalisation due to heart failure, particularly in those with pre-existing heart or kidney disease.

Review of Alogliptin (*Vipidia* and *Vipdomet*)

Marketing authorisation

Alogliptin (*Vipidia*) was the 5th dipeptidyl peptidase- 4 (DPP-4) inhibitor or gliptin to gain a UK marketing authorisation. It is authorised for the management of type 2 diabetes mellitus in adults to improve glycaemic control in combination with other glucose lowering therapies

when these together with diet or exercise, do not provide adequate glycaemic control. As well as a single component therapy in a variety of strengths, there is also a combination product available: alogliptin/metformin 12.5mg/1000mg tablet (*Vipdomet*). Authorised indications support dual therapy with metformin, sulfonylurea or pioglitazone and triple therapy with pioglitazone and metformin. Although alogliptin is authorised for use with insulin (with or without metformin), it is not authorised as monotherapy or as triple therapy with metformin and a sulfonylurea. A comparison of all five DDP-4 inhibitors reveals that sitagliptin still has the widest range of authorised indications:

Indication	**sitagliptin**	**saxagliptin**	**linagliptin**	**vildagliptin**	**alogliptin**
monotherapy	√	√	√	√	
Dual therapy					
metformin	√	√	√	√	√
sulfonylurea	√	√		√	√
glitazone	√	√		√	√
Triple therapy					
Sulfonylurea + metformin	√	√	√	√	
Glitazone + metformin	√				√
With insulin					
With insulin ± metformin	√	√	√	√	√
Indication	**sitagliptin**	**saxagliptin**	**linagliptin**	**vildagliptin**	**alogliptin**
Monotherapy	√	√	√	√	
Dual therapy					
with metformin	√	√	√	√	√
with sulfonylurea	√	√		√	√
with glitazone	√	√		√	√
Triple therapy					
with sulfonylurea + metformin	√	√	√	√	Safety and efficacy not yet confirmed.
with glitazone + metformin	√				√
with insulin					
with insulin ± metformin	√	√	√	√	√

Of the five DPP-4 inhibitors, alogliptin is the only one without a license for monotherapy. The manufacturer have chosen not to pursue a monotherapy license on commercial grounds; metformin is advocated as first-line therapy for patients with type 2 DM and over 93% of patients in the UK receive metformin is prescribed as part of their treatment regime.

PACEF Comment:
Alogliptin (Vipidia) does not hold a monotherapy license, but this is unlikely to be an issue in the vast majority of patients with DM who are receiving multi-component therapy. Sitagliptin is still the only DPP-4 inhibitor with the full range of licensed indications.

Comparative efficacy

Evidence of efficacy comes from a series of clinical trials where alogliptin at a dose of 25mg demonstrated good glycaemic control in terms of reduction of HbA1c levels compared to placebo in combination with oral hypoglycaemic agents. A longer term efficacy and safety trial undertaken over a period of two years demonstrated durability of control of the 25mg dose compared to glipizide treatment.

HbA1c reduction

There are no comparative data between any of the DPP-4 inhibitors in relation to HbA1c reduction. Results from a systematic review comparing efficacy of DPP-4 inhibitors in terms of HbA1c reduction in combination with metformin suggest that alogliptin performs at least as well as alternative agents.

Cardiovascular outcomes

Alogliptin also launched with positive cardiovascular outcomes data. Results from a 40 month study in type 2 diabetics known as the EXAMINE trial showed non-inferiority compared to placebo in terms of rates of major cardiovascular events in a population of high risk patients who had experienced an acute coronary event in the 90 days prior to enrolment in the study. A subsequent post-hoc analysis of the results of the EXAMINE trial showed a numerical increase in the alogliptin group in the rate of hospitalisation associated with heart failure compared to placebo, although these results did not reach statistical significance.

Saxagliptin is the only other DPP-4 inhibitor with cardiovascular outcome data. In SAVOR trial, saxagliptin was associated with an increased risk of hospitalisation due to heart failure; although this was a secondary endpoint, it did reach statistical significance.

A further trial published in June 2015 in the *New England Journal of Medicine* known as TECOS studied the use of sitagliptin in type 2 diabetics with cardiovascular disease and showed no increased risk of cardiovascular events or heart failure.

In response to these concerns, the American Food and Drug Administration (FDA) recently published a safety review of saxagliptin and alogliptin that identified a possible increased risk of hospitalisation for heart failure in patients taking these medicines who already have heart or kidney disease. As a result of this, additional warnings and precautions have been added to the labels of both these products in the USA. At this stage, it is too early to tell whether this is potentially a risk with all DPP-4 inhibitors or whether this is related solely to these two specific agents.

PACEF Comment

PACEF have reviewed the trial evidence linking alogliptin and saxagliptin to increased hospitalisation due to heart failure and acknowledge that there is a small increased risk, particularly in those with pre-existing heart or kidney disease. They also recognise that the increased risk in both drugs was identified through secondary endpoint data and only achieved statistical significance in the SAVOR trial involving saxagliptin. Nonetheless, when initiating new patients on alogliptin or switching existing patients to alogliptin, prescribers should be mindful of existing SPC advice which is to avoid in severe renal impairment and exercise caution in those with pre-existing heart failure. All patients taking alogliptin or saxagliptin (or any other DPP-4 inhibitor) should be advised to contact their healthcare professional right away if they develop the signs and symptoms of heart failure such as unusual shortness of breath during daily activities, breathing difficulties when lying down, tiredness, weakness, fatigue or weight gain with swelling of the ankles, feet, legs or stomach. The MHRA have not yet published on this issue, but may choose to do so imminently. Local guidance and switch protocols will be amended in accordance with any subsequent advice from the MHRA.

Renal Impairment

The table below summarizes the dose adjustments, cautions and contra-indications for each of the DPP-4 inhibitors in patients with renal or hepatic impairment:

	Alogliptin	**Linagliptin**	**Saxagliptin**	**Sitagliptin**	**Vildagliptin**
Renal impairment (creatinine clearance)7-11 Mild: >50 to <80 mL/min Moderate: ≥30 to ≤50 mL/min Severe: <30 mL/min End stage renal disease (ESRD) requiring dialysis: <15mL/min	Mild: no dose adjustment Moderate: 12.5mg once daily Severe: 6.25mg once daily ESRD requiring dialysis: 6.25mg once daily Peritoneal dialysis: the use of alogliptin has not been studied	No dose adjustment is required.	Mild: no dose adjustment Moderate: 2.5mg once daily Severe: 2.5mg once daily ESRD requiring dialysis: not recommended	Mild: no dose adjustment Moderate: 50mg once daily Severe: 25mg once daily ESRD requiring dialysis: 25mg once daily	Mild: no dose adjustment Moderate: 50mg once daily Severe: 50mg once daily ESRD requiring dialysis: 50mg once daily. Limited experience of vildagliptin in patients on haemodialysis – use with caution
Hepatic impairment	Not recommended in severe hepatic impairment (Child-Pugh score >9)	No dose adjustment required but clinical experience in such patients is lacking	Use with caution in patients with moderate hepatic impairment but no dose adjustment required for these patients. Not recommended in patients with severe hepatic impairment	No dose adjustment required for mild to moderate hepatic impairment, no studies have been done in patients with severe hepatic impairment	Do not use in patients with hepatic impairment including patients with pre-treatment ALT or AST three times the upper limit of normal

Ref: Luton Clinical Commissioning Group, *Standard Operating Procedures: Gliptins Prescribing Review* (July 2015).

PACEF Comment
All DPP-4 inhibitors can be used in mild renal impairment with no dose adjustment. In moderate to severe renal impairment, dosage adjustment is required except for linagliptin. Alogliptin can be used in moderate and end stage renal impairment with dose adjustments; it can also be used in all but severe hepatic impairment. For severe hepatic impairment the only option is linagliptin, although clinical experience in this patient group is limited.

Cost Comparison

PACEF Comment
A cost comparison of the different DPP-4 inhibitors (see above) reveals that alogliptin (*Vipidia*) is currently the lowest cost agent.

Potential savings from switching alternative DPP-4 inhibitors to alogliptin

Assuming 80% of patients taking alternative DPP-4 inhibitors are suitable for switch to alogliptin the annual savings for each of the Lincolnshire CCGs are as follows:

	Annual saving assuming 80% switch to alogliptin
Lincolnshire East CCG	£139,846
Lincolnshire West CCG	£79,318

South Lincolnshire CCG	£77,568
South West Lincolnshire CCG	£50,707
Lincolnshire	£347,439

PACEF Recommendation:

Alogliptin 6.25mg, 12.5mg and 25mg tablets (*Vipidia*) and alogliptin/metformin 12.5mg/1g tablets (*Vipdomet*) are already designated GREEN and approved for use through the *Lincolnshire Joint Formulary.* Even in patients with renal impairment, alogliptin can usually be prescribed, subject to recommended dosage adjustments, although it should be avoided in severe renal impairment (see above). Linagliptin (*Trajenta*) undergoes minimal elimination via the renal route, requires no dosage adjustment in renal and hepatic impairment and can be considered as a second line alternative to alogliptin in those with severe renal impairment or severe hepatic impairment. Care should be taken to ensure that linagliptin is not prescribed prematurely or inappropriately in patients with mild or moderate renal impairment where alogliptin (dose adjusted in moderate impairment) would be a more cost-effective choice. New patients requiring DPP-4 inhibitor therapy should be considered for alogliptin therapy first line. Existing patients currently taking alternative DPP-4 inhibitors should be considered for a therapeutic switch to an equivalent dose of alogliptin. Alogliptin switching has been incorporated in the Prescribing QIPP Programme for 2016/17 and a therapeutic switch protocol is in development with prescribing technician support available to practices wishing to undertake the switch. When initiating new patients on alogliptin or switching existing patients to alogliptin, prescribers should be mindful of existing SPC advice which is to avoid in severe renal impairment and exercise caution in those with pre-existing heart failure. All patients taking alogliptin or saxagliptin (or any other DPP-4 inhibitor) should be advised to contact their healthcare professional right away if they develop the signs and symptoms of heart failure such as unusual shortness of breath during daily activities, breathing difficulties when lying down, tiredness, weakness, fatigue or weight gain with swelling of the ankles, feet, legs or stomach.

In view of declining use, saxagliptin (*Onglyza*) has been removed from the *Lincolnshire Joint Formulary* designation RED-RED. Sitagliptin (*Januvia*) is still the DPP-4 inhibitor with the widest range of licensed indications and remains on the *Formulary* as a second line alternative to alogliptin. Vildagliptin (*Galvus*) is not recommended for use and remains RED-RED.

References

1. NICE NG 28 *Management of type 2 diabetes in adults* (December 2015)
2. United States Food and Drug Administration, Drug Safety Communication: *FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin* (May 2016).
3. Scirica B.M, Bhatt D.L, Braunwald E. et al., Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus. *New Eng J Med*. Oct 3rd 2013 (pp 1317-26).
4. White W.B, Cannon C.P, Heller S.R. et al., Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *New Eng J Med*. 369;14 October 3rd 2013 (pp1327-1335).
5. Z.Faiez, Cannon C.P, Cushman W.C et al., Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE; a multicentre randomised, double blind trial. *Lancet* Vol 385 May 23rd 2015.
6. Green J.B, Bethel M.A, Armstrong P.W et al., Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. Trial evaluating cardiovascular Outcomes with Sitagliptin (TECOS). *N.Eng J Med*. 2015, 373: July 16th 2015 (pp 232-242).
7. Filion K.B, Suissa S., DPP-4 inhibitors and heart failure: some reassurance, some uncertainty, *Diabetes Care* 2016.20016;39: (pp735-737).

8. Li L, Deng K, Liu J et al., Dipeptidyl peptidase -4 inhibitors and risk of heart failure in type 2 diabetes: systematic review and meta-analysis of randomised and observational studies. *BMJ* 2016 352i610.

Acknowledgements

Many thanks to: Cathy Johnson, Interface Lead Pharmacist, Arden GEM Commissioning Support Unit for her help with the preparation of this *Bulletin.* Also thanks to all members of the Diabetes Working Group, a sub-Group of PACEF, who kindly worked with us on the various drafts.

Stephen Gibson
Head of Prescribing and Medicines Optimisation (Lincolnshire)
Arden GEM Commissioning Support Unit

August 2016