Hertfordshire and West Essex Integrated Care System

NHS Hertfordshire and West Essex Integrated Care Board

Dipeptidyl peptidase-4 (DPP-4) inhibitors (Gliptins) in Adults with Type 2 Diabetes (T2DM)

- There are currently five DPP-4 inhibitors (sitagliptin, alogliptin, linagliptin, saxagliptin and vildagliptin) licensed in the UK for the management of adults with T2DM.
- Between the gliptins there are differences in costs, licensed indications, monitoring requirements, interactions, and the requirement for dose adjustment in renal and hepatic impairment. No comparative trials between the DPP-4 inhibitors have been conducted.
- Robust clinical outcome data for DPP-4 inhibitors, particularly around their cardiovascular effects and long-term safety in people with T2DM is limited.

DPP-4 inhibitor choice (Hertfordshire and West Essex Area Prescribing Committee – March 2023)

First choice – sitagliptin
Second choice – linagliptin **–** preferred for the following patients:

- Patients with severely impaired renal function (eGFR < 30 ml/min/1.73 m^2) including patients whose eGFR is expected to be < 30 ml/min/1.73 m^2 within a year.
- Patients who have had a previous episode of Acute Kidney Injury (AKI).

Note: Where patients meet criteria for SGLT-2 inhibitor use in chronic kidney disease (CKD), consider SGLT-2 inhibitor first as SGLT-2 inhibitors have demonstrated cardiovascular benefit, DPP4 inhibitors show cardiovascular safety but not cardiovascular benefit.

NICE NG 28 (T2DM in Adults) – Recommendations on DPP-4 inhibitor use

- Monotherapy – A DPP-4 inhibitor can be initiated if:
  - Metformin is contraindicated or not tolerated, and the person does not have chronic heart failure or established atherosclerotic cardiovascular disease or is not at high risk of developing cardiovascular disease.
  - Metformin and SGLT-2 inhibitors are contraindicated or not tolerated, and the person has chronic heart failure or established atherosclerotic cardiovascular disease or is at high risk of developing cardiovascular disease.
- Dual or triple therapy – A DPP-4 inhibitor can be added if treatment with metformin and/or another oral drug (sulfonylurea, pioglitazone or SGLT2 inhibitor) has not continued to control HbA1c to below the person's individually agreed threshold for further intervention.

Comparative data on DPP-4 inhibitors

Drug	Standard dose & 28-day cost (as per July 2023 Drug Tariff)	Monotherapy	Dual Therapy			Triple Therapy			Addition to insulin (+/- metformin)	CV outcome data from large RCT (see summary below)	Hepatic impairment	Renal impairment
			+ metformin	+ sulfonylurea	+ pioglitazone	+ metformin + sulfonylurea	+ metformin + pioglitazone	+ metformin + ertugliflozin				
Sitagliptin	100mg daily **£19.49**	✓	✓	✓*	✓	✓*	✓	✓^	✓*	✓ (TECOS)	No clinical experience in severe hepatic impairment (Child-Pugh score > 9)	eGFR ≥ 30 to < 45 mL/min/1.73 m^2: 50mg once daily. eGFR < 30 mL/minute/1.73 m^2: 25mg once daily.

This HWE APC recommendation is based upon the evidence available at the time of publication.
The recommendation will be reviewed upon request in the light of new evidence becoming available.

Linagliptin	5mg daily **£33.26**	✓	✓	✗	✗	✓*	✗	✓^	✓*	✓ (CARMELINA)	No dose adjustment but lack of clinical experience	No dose adjustment
Alogliptin	25mg daily **£26.60**	✗	✓	✓*	✓	✗	✓**	✓^	✓*	✓ (EXAMINE)	Not recommended in severe hepatic impairment (Child-Pugh score > 9)	eGFR ≥ 30 to ≤ 50 mL/min/1.73 m^2: 12.5mg once daily. eGFR < 30 mL/min/1.73 m^2: 6.25mg once daily.
Saxagliptin	5mg daily **£31.60**	✓	✓	✓*	✓	✓*	✗	✓^	✓*	✓ (SAVOR-TIMI 53)	Caution in moderate hepatic impairment. Not recommended in severe hepatic impairment.	eGFR < 45 mL/min/1.73 m^2: 2.5mg once daily. Not recommended in end-stage renal disease requiring haemodialysis.
Vildagliptin	50mg twice daily **£29.10**	✓	✓	✓*†	✓	✓*	✗	✓^	✓*	✗	Not recommended in hepatic impairment, including patients with pre-treatment ALT or AST > 3x the upper limit of normal	eGFR < 50 mL/min/1.73 m^2: 50mg once daily Caution in end-stage renal disease on haemodialysis.

***** = consider a lower dose of sulfonylurea / insulin ** = consider a lower dose of metformin / pioglitazone **†** = Reduce dose of vildagliptin to 50mg once daily
^ = off-label but recommended in line with NICE TA583

Cardiovascular Outcome Data from Large Randomised Controlled Trials

- TECOS evaluated the cardiovascular safety of sitagliptin versus placebo in patients with T2DM with established cardiovascular disease. After a median follow up of 3 years, sitagliptin, when added to usual care, did not increase the risk of major adverse cardiovascular events or the risk of hospitalisation for heart failure compared to usual care without sitagliptin in patients with T2DM.
- CARMELINA evaluated the cardiovascular and renal safety of linagliptin versus placebo in patients with T2DM and with increased CV risk evidenced by a history of established macrovascular or renal disease. After a median follow up of 2.2 years, linagliptin, when added to usual care, did not increase the risk of major adverse cardiovascular events or renal outcome events. There was no increased risk in hospitalization for heart failure compared to usual care without linagliptin in patients with T2DM.
- EXAMINE evaluated the cardiovascular safety of alogliptin versus placebo, in addition to standard of care, in patients with T2DM and a recent acute coronary syndrome. After a median follow up of 18 months, the rates of major adverse cardiovascular events were not increased with alogliptin as compared with placebo.
- SAVOR-TIMI 53 evaluated the cardiovascular efficacy and safety of saxagliptin when added to standard of care in patients with T2DM who are at high risk for cardiovascular events (established cardiovascular disease and/or multiple risk factors). After a median follow up of 2 years, saxagliptin did not increase or decrease the rate of ischaemic events, though the rate of hospitalisation for heart failure was increased.

Common Side Effects

Sitagliptin – Headache
Alogliptin – Abdominal pain; gastrooesophageal reflux disease; headache; increased risk of infection; skin reactions
Linagliptin – No common side effects reported.
Saxagliptin – Abdominal pain; dizziness; fatigue; headache; increased risk of infection; skin reactions; vomiting
Vildagliptin – Dizziness

Drug Interactions

All DPP-4 inhibitors (Sitagliptin, Alogliptin, Linagliptin, Saxagliptin and Vildagliptin)

- The dose of concomitant sulfonylurea or insulin may need to be reduced when used in combination with DPP-4 inhibitors due to an increased risk of hypoglycaemia.
- Blood glucose-lowering effects of DPP-4 inhibitors may be enhanced by: Alcohol, anabolic steroids, monoamine oxidase inhibitors (MAOIs) and testosterone.
- Blood glucose-lowering effects of DPP-4 inhibitors may be antagonized by: Corticosteroids, diuretics (thiazide and related, and loop) and oestrogens/progestogens.

Sitagliptin

- It is possible that potent CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, ritonavir, clarithromycin) could alter the phamacokinetics of sitagliptin in patients with severe renal impairment or end-stage renal disease.
- Sitagliptin increases plasma concentration of digoxin. No dose adjustment of digoxin is recommended. Patients at risk should be monitored for digoxin toxicity.

Saxagliptin

- CYP3A4/5 inducers (e.g. carbamazepine, dexamethasone, phenobarbital, phenytoin, and rifampicin) may decrease plasma concentration of saxagliptin and reduce the glycaemic lowering effect.
- Plasma concentrations of saxagliptin may be increased by CYP3A4/5 inhibitor ketoconazole.

Linagliptin

- Full efficacy of linagliptin in combination with potent inducers of P-glycoprotein and CYP3A4 (e.g. rifampicin, carbamazepine, phenobarbital and phenytoin) might not be achieved, particularly if these are administed long-term.

Vildagliptin

- There may be an increased risk of angioedema in people taking vildagliptin and ACE-inhibitors concomitantly.

NB: This list is not exhaustive; please refer to BNF/SPC for further information.

US Food and Drug Administration (FDA) Safety Review (April 2016)

- A US FDA safety review reported that alogliptin and saxagliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease.
- The recommendation is that healthcare professionals should consider discontinuing alogliptin/saxagliptin in patients who develop heart failure and monitor their diabetes control.

Drug Safety Update (September 2012)

- Patients treated with DPP-4 inhibitors should be informed of the characteristic symptoms of acute pancreatitis – persistent, severe abdominal pain (sometimes radiating to the back) and encouraged to tell their healthcare provider if they have such symptoms.
- If pancreatitis is suspected, the DPP-4 inhibitor and other potentially suspect medicines should be discontinued.
- Report suspected adverse reactions through the Yellow Card Scheme - see www.yellowcard.gov.uk.

References

1. Sitagliptin, Alogliptin, Linagliptin, Saxagliptin, Vildagliptin Summary of Product Characteristics available at www.medicines.org.uk
2. eMC Dictionary of Medicines and Devices Browser http://dmd.medicines.org.uk/DesktopDefault.aspx?tabid=1
3. NICE NG28 Type 2 diabetes in adults: management https://www.nice.org.uk/guidance/ng28
4. NICE TA 583 Ertugliflozin with metformin and a dipeptidyl peptidase-4 inhibitor for treating type 2 diabetes June 2019. https://www.nice.org.uk/guidance/ta583
   NICE BNF at https://bnf.nice.org.uk/ Last updated: November 2022
5. TECOS – Green, J., Bethel, A., Armstrong, P., Buse, J., Engel, S., Garg, J., Josse, R., Kaufman, K., Koglin, J., Korn, S., Lachin, J., McGuire, D., Pencina, M., Standl, E., Stein, P., Suryawanshi, S., Van de Werf, F., Peterson, E., and Holman, R. (2015). Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. New England Journal of Medicine (2015) https://www.nejm.org/doi/full/10.1056/nejmoa1501352
6. EXAMINE – White, W., Cannon, C., Heller, S., Nissen, S., Bergenstal, R., Bakris, G., Perez, A., Fleck, P., Mehta, C., Kupfer, S., Wilson, C., Cushman, W., and Zannad, F. (2013). Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes. New England Journal of Medicine (2013) https://www.nejm.org/doi/full/10.1056/nejmoa1305889
7. CARMELINA – Rosenstock, J., Perkovic, V., Johansen, OE., Cooper, M., Kahn, S., Marx, N., Alexander, J., Pencina, M., Toto, R., Wanner, C., Zinman, B., Woerle, HJ., Baanstra, D., Pfarr, E., Schnaidt, S., Meinicke, T., George, J., von Eynatten, M., and McGuire, D. (2019). Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk. The Journal of the American Medical Association (2019) https://jamanetwork.com/journals/jama/fullarticle/2714646
8. SAVOR-TIMI 53 – Scirica, B., Bhatt, D., Braunwald, E., Steg, G., Davidson, J., Hirshberg, B., Ohman, P., Frederich, R., Wiviott, S, Hoffman, E., Cavender, M., Udell, J., Desai, N., Mosenzon, O., McGuire, D., Ray, K., Leiter, L., and Raz, I. (2013). Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus. New England Journal of Medicine (2013) https://www.nejm.org/doi/full/10.1056/nejmoa1307684
9. MHRA Drug Safety Update September 2012 http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON185628
10. FDA Safety Review April 2016 http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm494252.htm

Version	2.1 Update following June 2024 HWE APC decision to adopt NICE NG28 treatment algorithm for type 2 diabetes in adults.
Developed by	Pharmacy and Medicines Optimisation Team, Hertfordshire and West Essex (HWE) ICB with relevant HWE ICS stakeholders.
Approved by	Hertfordshire & West Essex Area Prescribing Committee
Date approved / updated	Updated September 2024
Review date	This HWE APC recommendation is based upon the evidence available at the time of publication. This recommendation will be reviewed upon request in the light of new evidence becoming available.
Superseded version	2.0 – Update to the Hertfordshire Medicines Management Committee (HMMC) DPP-4 inhibitor (gliptins) comparison document (March 2023 update to version 1.0 June 2016)