

### DPP-4 inhibitors (Gliptins) in Adults with Type 2 Diabetes

- There are currently five dipeptidyl peptidase-4 (DPP-4) enzyme inhibitors ('gliptins') licensed in the UK for the management of type 2 diabetes (T2DM).
- No comparative trials between the DPP-4 enzyme inhibitors have been conducted.
- There are a number of differences between the gliptins including costs, licensed indications, monitoring requirements, interactions and the need for dose adjustment in renal and hepatic impairment
- Robust clinical outcome data for gliptins, particularly around their cardiovascular effects and long-term safety in people with type 2 diabetes is limited.

#### Hertfordshire Medicines Management Committee Recommendations on DPP-4 enzyme inhibitor choice:

**New Patients:** Alogliptin is recommended within license for new patients requiring gliptin therapy, unless the patient has impaired renal function. In these circumstances, linagliptin is the agent of choice as no dosage adjustment is required.

**Existing Patients:** Alogliptin may be considered as an option for patients on an alternative DPP-4 inhibitor within specific inclusion, exclusion and follow-up criteria as agreed by individual CCGs. HVCCG Position Statement available. Specialists must give clear rationale for choice of alternative DPP-4 inhibitor.

#### NICE Clinical Guideline Recommendation (NG 28)

NICE makes recommendations for when DPP-4 inhibitors can be considered in adults with type 2 diabetes:

- If metformin is contraindicated or not tolerated, consider initial drug treatment with a dipeptidyl peptidase-4 (DPP-4) inhibitor or pioglitazone or a sulfonylurea.
- If initial drug treatment with metformin has not continued to control HbA1c to below the person's individually agreed threshold for intensification/if metformin is contraindicated or not tolerated, consider dual therapy with metformin and a DPP 4 inhibitor or metformin and pioglitazone or metformin and a sulfonylurea.
- if dual therapy with metformin and another oral drug has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider either triple therapy with metformin, a DPP 4 inhibitor and a sulfonylurea or metformin, pioglitazone and a sulfonylurea

**DPP-4 inhibitor therapy should only be continued if the person has a reduction of at least 5.5 mmol/mol [0.5%] in HbA1c in 6 months.**

#### Comparative data on available DPP-4 inhibitors (Gliptins)

	28 day cost for standard daily doses	Mono-therapy	With Insulin (+/- MET)	Dual Therapy with MET	Dual Therapy with SU	Dual Therapy with PIO	Triple therapy with MET & SU or PIO	CV outcome data from large RCT	Hepatic impairment	Renal impairment (CrCl ml/min)		
										>50 MILD	≥30-50 MODERATE	<30 SEVERE
<b>Alogliptin</b>	25mg daily £26.60	X	√*	√	√	√	√(with MET & PIO only)	√ (see overleaf)	No dose adjustment, mild to mod. No experience in severe disease	25mg daily	12.5mg daily (£26.60)	6.25mg daily (£26.60)
<b>Linagliptin</b>	5mg daily £33.26	√**	√*	√	X	X	√* (with MET & SU only)	X	No dose adjustment ***	5mg daily	5mg daily (No dose adjustment)	
<b>Saxagliptin</b>	5mg daily £31.60	√**	√*	√	√* / **	√	√* (with MET & SU only)	√ (see overleaf)	No dose adjustment, mild to mod. Caution in mod. Not recommended in severe disease	5mg daily	2.5mg daily (£31.60)	2.5mg daily (use with caution; not recommended in ESRD requiring haemodialysis)
<b>Sitagliptin</b>	100mg daily £33.26	√**	√*	√	√* / **	√	√*	X	No dose adjustment, mild to mod. No experience in severe disease	100mg daily	50mg daily (£33.26)	25mg daily (£33.26)
<b>Vildagliptin</b>	50mg twice daily £33.35	√**	√*	√	√* / ** (Reduce dose to 50mg daily)	√	√* (with MET & SU only)	X	Should <b>not</b> be used in patients with hepatic impairment, <b>including</b> patients with pre-treatment ALT or AST > 3x the upper limit of normal ****	50mg twice daily	50mg daily (£16.68)	50mg daily (use with caution in ESRD)

MET= metformin SU= sulphonylurea PIO= pioglitazone ESRD= end-stage renal disease on haemodialysis \*= consider a lower dose of SU/ insulin to prevent hypoglycaemia

### **Cardiovascular Outcome Data from Large Randomised Controlled Trials**

- All gliptins have cardiovascular outcome RCTs in progress and those for saxagliptin, alogliptin and sitagliptin have reported.
- SAVOR compared the addition of saxagliptin or placebo to other blood-glucose-lowering medication in T2DM and demonstrated that at around 2 years, saxagliptin did not increase or reduce the risk of cardiovascular outcomes, but increased the risk of hypoglycaemia and may also have increased the risk of admission to hospital because of heart failure.
- EXAMINE compared the addition of alogliptin or placebo to other blood-glucose-lowering medication in T2DM and demonstrated that at a median follow up of 18 months, alogliptin did not increase or reduce the risk of cardiovascular outcomes.
- TECOS compared the addition of sitagliptin or placebo to other blood-glucose-lowering medication in T2DM and demonstrated that at around 2 years, sitagliptin had a numerically lower risk of admission related to heart failure, although this was not statistically significant.

### **FDA Safety Review April 2016**

- An FDA safety review has found that type 2 diabetes medicines containing saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease.

### **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](http://www.yellowcard.gov.uk).

### **Drug Interactions**

#### **To reduce the risk of hypoglycaemia a lower dose of sulphonylurea or insulin may be considered when used in combination with DPP-4 enzyme inhibitors.**

*Sitagliptin* - it is possible that potent CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, ritonavir, clarithromycin) could alter the pharmacokinetics of sitagliptin in patients with severe renal impairment or ESRD.

- Sitagliptin has a small effect on plasma digoxin concentrations. No dose adjustment of digoxin is recommended. Patients at risk should be monitored for digoxin toxicity.

*Saxagliptin* - Using CYP3A4 inducers like carbamazepine, dexamethasone, phenobarbital, phenytoin, and rifampicin may reduce the glycaemic lowering effect of saxagliptin.

*Linagliptin* - Full efficacy of linagliptin in combination with potent inducers of P-glycoprotein and CYP3A4, such as rifampicin, carbamazepine, phenobarbital and phenytoin might not be achieved, particularly if these are administered long-term.

*Vildagliptin/Alogliptin* – No clinically significant CYP450 mediated drug interactions.

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

### **Cost of 28 days supply of metformin with DPP-4 enzyme inhibitors (including combination products)**

- Each of the gliptins is available in a combination product with a fixed dose of metformin. The cost of the combination product in all cases is the same as the cost of the gliptin by itself with sitagliptin, saxagliptin, linagliptin and alogliptin. The cost of vildagliptin + metformin combination product is lower than vildagliptin alone.

### **References**

1. Sitagliptin, Saxagliptin, Linagliptin, Vildagliptin Summary of Product Characteristics available at [www.medicines.org.uk](http://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. BNF Sept 2013 – Mar 2014
5. NICE MPC KTT12 Type 2 diabetes mellitus <http://www.nice.org.uk/mpc/keytherapeutictopics/KTT12.jsp>
6. MHRA Drug Safety Update September 2012 <http://www.mhra.gov.uk/SafetyInformation/DrugSafetyUpdate/CON185628>
7. FDA Safety Review April 2016 <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm494252.htm>
8. NICE Medicines Evidence Commentary – Type 2 diabetes: study finds no benefit from saxagliptin on cardiovascular outcomes <http://arms.evidence.nhs.uk/resources/hub/1029671/attachment>
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