Commissioning Support
DPP-4 inhibitors

Sitagliptin (Januvia®), Vildagliptin (Galvus®), Saxagliptin (Onglyza®), Linagliptin (Trajenta®), Alogliptin (Vipidia®)

For the treatment of type 2 diabetes

Commissioning guidance points for consideration:

- NICE guidance on the management of patients with type 2 diabetes (NG28; updated 2017) involves an individualised, multifactorial approach that focusses on patient education, dietary advice, managing cardiovascular (CV) risk, managing blood glucose levels and identifying and managing long-term complications. In older people, also consider the likelihood of comorbidities, risks from polypharmacy, and their ability to benefit from long-term interventions because of reduced life expectancy.
- DPP-4is are included at all stages of the NICE diabetes algorithm. If a DPP-4i is appropriate, it is advised that the selection be based on the appropriate licensed indications, with the lowest acquisition cost.
- Four large, placebo-controlled trials evaluating mortality and CV outcomes with the DPP-4is (sitagliptin, saxagliptin, alogliptin and linagliptin), found no significant differences in the incidence of Major Adverse CV Events (MACE) with DPP-4is *vs*. placebo. Hospitalisation for heart failure (as a component of a pre-specified secondary endpoint) was significantly higher in saxagliptin-treated patients than with placebo (SAVOR-TIMI trial 3.5% *vs*. 2.8%; hazard ratio 1.27; 95% CI 1.07 to 1.51; p = 0.007). This outcome was not significantly different in trials evaluating sitagliptin (TECOS), alogliptin (EXAMINE) or linagliptin (CARMELINA). We did not find a CV outcome trial evaluating vildagliptin.
- Commissioners should ensure that adequate review/audit arrangements are in place to monitor metabolic response in patients treated with DPP-4is or other oral antidiabetic drugs covered by NICE guidance.
- NHS Digital has published a Guide to Quality Improvement in Specialist Diabetes services, based on data from the National Diabetes Audit. The guideline highlighted some priority issues for improvement including:
  - Poorer rates of care-process completion and treatment-target achievement in the under 65s
  - Inpatient onset severe hypoglycaemia and DKA/HHS (diabetic ketoacidosis/hyperglycaemic hyperosmolar state)
  - Poor pre-pregnancy care and antenatal care
  - Tortuous or absent diabetes foot-care pathways for treatment and secondary prevention of diabetic foot ulcers

MTRAC considered the DPP-4 inhibitors as a class to place them in context in the treatment of type 2 diabetes

Description of the technology

The dipeptidyl peptidase 4 (DPP-4) inhibitors act on DPP-4, an enzyme responsible for the inactivation of the incretin hormones including glucagon-like peptide 1 and glucose-dependent insulinotropic peptide, which are released from gut cells in response to a meal. These hormones stimulate insulin release and reduce glucagon secretions thereby reducing blood glucose levels.

Five DPP-4 inhibitors are licensed for use for the treatment of type 2 diabetes in the UK; their licensed indications are summarised in the Table overleaf.

Clinical evidence for efficacy and safety

Two network meta-analyses[1 2] evaluating CV and mortality outcomes for newer antidiabetic drugs (DPP-4is, SGLT2is and GLP-1s) *versus* older treatments (sulfonylureas and thiazolidinediones) found no significant difference for DPP-4is *versus* placebo for the rates of all-cause mortality, CV mortality and hospitalisation for heart failure (HF). The SGLT2is and GLP-1ras were associated with significantly lower rates of all-cause mortality and CV mortality than placebo, and SGLT2is showed significantly lower rates that DPP-4is.

CV safety of four DPP-4is compared with placebo was evaluated in large open-label safety trials: TECOS (sitagliptin)[3], CARMELINA (linagliptin)[4], SAVOR-TIMI (saxagliptin)[5] and EXAMINE (alogliptin)[6].

All four trials recruited participants with type 2 diabetes and existing CV disease (major coronary artery disease, ischaemic cerebrovascular disease, or atherosclerotic peripheral arterial disease), or at higher risk of developing CV disease. In addition, participants in the CARMELINA trial had an increased risk of renal disease[4]. There were differences between the trials relating to the participants' baseline HbA_{1c} and use of concomitant medications; all the trials allowed additional background treatment (diabetes treatment, hypertensive medications etc.).

These time-to-first-event trials all measured a composite outcome of CV death, non-fatal myocardial infarction (MI) or non-fatal stroke (Major Adverse Cardiovascular Events, or MACE). The TECOS trial also measured hospitalisation for unstable angina as part of the MACE outcome. The CARMELINA trial also measured a composite of renal outcomes: end-stage renal disease (ESRD), death due to renal failure, or a sustained decrease of ≥40% in eGFR (estimated glomerular filtration rate) from baseline. Secondary outcomes across the trials were the individual components of the MACE outcome, and safety outcomes e.g.incidence of pancreatitis.

MACE results: all DPP-4is were non-inferior to placebo, with actual event rates (similar with both placebo and

active treatment) from 11 to 12% for linagliptin, sitagliptin, and alogliptin and 7% in the saxagliptin trial.

Hospitalisation for HF: In the SAVOR-TIMI trial, this outcome was significantly higher in saxagliptin-treated patients than with placebo (3.5% *vs*. 2.8%; hazard ratio 1.27; 95% confidence interval [CI] 1.07 to 1.51; p = 0.007). There was no significant difference reported in the TECOS, EXAMINE or CARMELINA trials. A meta-analysis of these outcome trials also found no significant increase in hospitalisation for HF.

Composite renal outcome: there was no significant difference reported between linagliptin and placebo with incidences of 4.89 and 4.66 per 100 person-years respectively.

Table: Licensed indications of DPP-4 inhibitors available in the UK

Drug treatment: Usual daily doses quoted. A lower dose of a sulfonylurea or insulin may be necessary in combination with a DPP4i. Moderate renal impairment: consider a lower dose (except linagliptin); see SPCs for details.	**Monotherapy** in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance	**Dual oral therapy in combination with:**			**Triple oral therapy in combination with:**			**Add-on to insulin** (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control
		Metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin	**Sulfonylurea (SU)** in patients with insufficient glycaemic control despite maximal tolerated dose of a SU and for whom metformin is inappropriate due to contraindications or intolerance	**Thiazolidinedione**, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate	**Sulfonylurea and metformin** when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control	**Thiazolidinedione and metformin** when use of a thiazolidinedione is appropriate and when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control	**SGLT2 inhibitor and metformin** D = dapagliflozin, E = empagliflozin	
Sitagliptin 100mg (Januvia)	✓	✓	✓	✓	✓	✓	✗	✓
Vildagliptin 100mg (Galvus)	✓	✓	✓	✓	✓	✗	✗	✓
Saxagliptin 5 mg (Onglyza)	✓	✓	✓	✓	✓	✗	D	✓
Linagliptin 5mg (Trajenta)	✓	✓	✓	✗	✓	✗	E	✓
Alogliptin 25mg (Vipidia)	✗	✓	✓	✓	✓	✓	-[b]	✓

[a] *The doses shown do not represent the full range that can be used, and they do not imply therapeutic equivalence.*
[b] *Alogliptin has a general 'add-on license' indication for use in dual or triple therapy, but has not been studied in combination with a SGLT2i*

Safety and tolerability

A systematic review of longer-term safety of DPP-4is (up to 104 weeks) reported no significant difference in ***adverse event rates*** or discontinuation from treatment due to an adverse event between DPP-4is and comparators[7]. The review also found no significant difference in rates of hypoglycaemia between DPP-4is and comparators unless co- administered with a sulfonylurea or insulin, where the rate was higher. This is a known risk and is reflected in the dosing guidance (links in Table).

In September 2012, the MHRA described an increased ***risk of acute pancreatitis*** with use of approved inhibitors in post-marketing reports and clinical data. Reporting rates for pancreatitis with DPP-4is ranged from 1/1000 to 1/100 patients receiving the drug. A 2013 EMA review of findings concerning pancreatitis and precancerous, pancreatic duct metaplasia in patients with type 2 diabetes treated with DPP-4is concluded, "Presently available data do not confirm recent concerns over an increased risk of pancreatic adverse events with these medicines."

A pooled analysis of the incidence of acute pancreatitis used data from three of the CV outcome trials[8] (SAVOR-TIMI[5], TECOS[3] and EXAMINE[6]). Whilst the individual trials showed no significant differences in pancreatitis incidence, the pooled analysis showed an overall incidence that was significantly greater with DPP-4i-treatment than with placebo (OR 1.79 [95% CI 1.13 to 2.82], p = 0.013); absolute risk increase = 0.13%.

Two systematic reviews of the ***incidence of fractures*** with DPP-4i treatment found no significant difference for DPP-4is as a class *vs*. placebo using direct comparisons[9 10]. One of the reviews found a lower risk of fracture with alogliptin *vs*. placebo, saxagliptin and linagliptin using indirect comparisons.[9]

Considerations for the NHS

In the West Midlands, there are 280,912 patients with diabetes mellitus QOF disease registers in 2017/18[11], of which 90% will have type 2 diabetes. Current costs for a years' treatment are listed below:

- Alogliptin (Vipidia®) 25mg tablet £347
- Linagliptin (Trajenta®) 5mg tablet £434
- Saxagliptin (Onglyza®) 5mg tablet £412
- Sitagliptin (Januvia®) 100mg tablet £434
- Vildagliptin (Galvus ®) 50mg tablet £435

Prices from (MIMs, July 2019)

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