Prescribing Clinical Network *Surrey (East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG & Surrey Heath CCG), Crawley CCG and Horsham & Mid-Sussex CCG*

Summary of rationale for preferred choices of hypoglycaemic agents for the management of type 2 diabetes

Gliptins (DPP-4 inhibitors)- Preferred choice – UPDATED June 2022

Summary –Sitagliptin is the preferred gliptin (DPP-4) of choice for use within Surrey.

- NICE and MTRAC advise selecting a DPP-4 inhibitor based on lowest acquisition cost, where all other factors are equal
- There are no clinically important differences in efficacy between the DPP-4 inhibitors.
- In RCTs, sitagliptin has not been shown to have adverse cardiovascular outcomes

Efficacy	**Safety**
Meta-analyses show that all the gliptins provide similar, modest HbA1c reduction of about 0.5–1% with monotherapy[1,2] There may be additive effects of HBA1c reduction from combination therapy with other antihyperglycaemic agents[3]DPP-4 inhibitors compared with sulfonylureas or pioglitazone suggest, at best, equivalent HbA1c control and slightly improved weight profile, but treatment failure with DPP-4 inhibitors was more common.[1] **Cardiovascular (CV) outcome data** DPP-4 inhibitors have proven cardiovascular safety but have not been shown to improve cardiovascular outcomes in four large placebo controlled RCTs (Saxagliptin in SAVOR-TIMI 53, Alogliptin in EXAMINE, Sitagliptin in TECOS and Linagliptin in CARMELINA[4,8]	DPP-4 inhibitors have a good safety and tolerability profile[2.] The adverse effects of the DPP-4's are broadly similar. A higher rate of hospitalisations for heart failure was reported with Saxagliptin in the SAVOR-TIMI 53 study (3.5% vs 2.8%; HR 1.27, 95% CI 1.07 to 1.51). There was a numerical, non-significant increase hospitalisation due to heart failure with Alogliptin in EXAMINE. There was no significant difference seen with sitagliptin in TECOS and linagliptin in CARMELINA[4,8] The SPCs for Saxagliptin and Alogliptin advise using them with caution in patients with heart failure (NHYA class III or IV), and Saxagliptin also has cautions about use in patients at risk of hospitalisation for heart failure. FDA safety review reports Saxagliptin and Alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease so recommends health professionals consider discontinuing Saxagliptin and Alogliptin in patients who develop heart failure and monitor their diabetes control.[4] MHRA reported an increased risk of acute pancreatitis for all DPP-4 inhibitors, the risk is low (ranging between 1/1 000 and 1/100 patients receiving the drug9). FDA warns that Sitagliptin, Saxagliptin, Linagliptin, and Alogliptin may be associated with potentially severe and disabling joint pain[7]– class effect (note vildagliptin not available in US) See individual SPCs for further information on contraindications/ interactions/ side effects

See accompanying document : PCN – Comparison of the commonly prescribed antidiabetic treatments for further detail on licensed combinations and use in renal and hepatic impairment

Patient / Other factors	**Cost** (28 days treatment – Drug Tariff. Prices correct as of May 2022)
Sitagliptin can be safely used in all degrees of renal impairment as per dosing below[9] • GFR ≥ 45mL/min: 100mg once daily • GFR ≥ 30 to < 45 mL/min: 50mg once daily • GFR ≥ 15 to <30 mL/min: 25mg once daily • End-stage renal disease (GFR < 15 mL/min), including haemodialysis or peritoneal dialysis: 25mg once daily The DPP-4 inhibitors are available as combination products with metformin and empagliflozin; however, these should only be considered once a patient is stabilised on a dose and treatment has been evaluated. The combination products are all fixed dose combination products and are therefore inappropriate to use in any patients stabilised on a different dose. [10]	Alogliptin 25mg daily £26.60 Saxagliptin 5mg daily £31.60 Linagliptin 5mg daily £33.26 Sitagliptin 100mg daily £33.26 (Projected 80% cost reduction from end 2022) Vildagliptin 50mg BD £33.35 (Projected 80% cost reduction after end 2022) Sitagliptin is expected to be available generically from the end of 2022 with a projected 80% cost reduction. Linagliptin will not be available generically until August 2026. DPP-4 inhibitors have a flat pricing structure across strengths and therefore doses should be optimised to the fewest number of tablets taken. [10]

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SGLT-2 - Preferred choice

Summary –The PCN should consider Empagliflozin as the SGLT-2 of preferred choice for use within Surrey.

- NICE recommends SGLT-2 inhibitors as a treatment option for type 2 diabetes.
- In a RCT, empagliflozin has been shown to reduce rates of cardiovascular events (although could be a class effect).
- Dapagliflozin should not be used in combination with pioglitazone, and canagliflozin has been linked with an increased risk of lower limb amputation and increased risk of bone fractures.
- Empagliflozin is licensed for use in people up 84 years old.

Efficacy

NICE have approved the following SGLT2 inhibitors for the treatment of type 2 diabetes[3,4,5,6,7].

- Empagliflozin in combination therapy for treating type 2 diabetes. TA336; Mar 2015
- Dapagliflozin in combination therapy for treating type 2 diabetes. TA288; June 2013
- Dapagliflozin in triple therapy for treating type 2 diabetes. TA418; Nov 2016
- Canagliflozin in combination therapy for treating type 2 diabetes. TA315; June 2015
- Canagliflozin, dapagliflozin and empaglflozin as monotherapies for treating type 2 diabetes. TA390; May 2016.

Although all three SGLT2 inhibitors have been given positive NICE technology appraisals, only empagliflozin has evidence to show positive cardiovascular outcomes[8]. This may be a class effect of the drugs. Results of CV outcomes studies with other SGLT-2 inhibitors are awaited.

Safety

The adverse reactions of SGLT-2 inhibitors are broadly similar. The most common adverse drug reactions are hypoglycaemia & urogenital infection (UTIs, candidal infection), although this isn't usually a reason to discontinue treatment. Adverse drug reactions related to volume depletion (dehydration, hypovolaemia, hypotension) have been reported. MHRA have warned of the risk of Diabetic Ketoacidosis with all SGLT-2 inhibitors in June 2015 and again in April 2016. Available at: https://www.gov.uk/drug-safety-update/sglt2-inhibitors-canagliflozin-dapagliflozin-empagliflozin-risk-of-diabetic-ketoacidosis

In March 2017 the MHRA warned that canagliflozin increased the risk of lower-limb amputation (mainly toes) in patients with type 2 diabetes. Evidence does not show an increased risk for dapagliflozin and empagliflozin, but the risk may be a class effect. Preventive foot care is important for all patients with diabetes [9]

An increased risk of bone fractures has been reported with canagliflozin, and decreases in bone mineral density at the hip and lumbar spine [10].

See individual SPC for further information on contraindications/interactions/side effects[2]

Patient factors

Dapagliflozin should not be used in combination with pioglitazone (theoretical increased risk of bladder cancer) [2]

There is limited experience of using SGLT-2 inhibitors in the elderly. Dapagliflozin is not recommended in patients over 75 years, empagliflozin is not recommended in patients > 85 years old and canagliflozin should be used with caution particularly in > 75 years old [2].

Cost

28 day cost for all SGLT- 2 inhibitors is the same. (All of the SGLT2 inhibitors are available co-formulated with metformin at no additional cost).

£ 36.59

See accompanying document : PCN – Comparison of the commonly prescribed antidiabetic treatments for further detail on licensed combinations and use in renal and hepatic impairment

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GLP-1 receptor agonists (GLP-1 RA) - Preferred choice

Summary –The PCN should consider lixisenatide, liraglutide and dulaglutide as preferred GLP-1 receptor agonists.

- NICE advises selecting GLP-1 receptor agonist based on lowest acquisition cost, where all other factors are equal
- There are no robust direct head to head comparisons of GLP-1 receptor agonists. There may be small differences between GLP-1s .in improving glycaemic control, and weight reduction, but we do not know how this translates into improved patient orientated outcomes.
- In an RCT, liraglutide has been shown to reduce rates of cardiovascular events.
- Local preferred choices are lixisenatide (lowest acquisition cost), liraglutide (widely used, dose adjustment not required in severe renal impairment and has RCT data to show improved CV outcomes), and dulaglutide (widely used once weekly preparation).
- GLP-1 receptor agonists are recommended to be used in accordance with NICE guidelines. Treatment should be reviewed at 6 months. If there is no beneficial metabolic response (defined in NICE guidance), then stop treatment, and consider alternative treatment (usually insulin initiation) in line with NICE guidance.

Efficacy

NICE Guideline Development Group commented that based on the evaluated evidence, they were not convinced of the purported material differences between the various GLP-1 mimetic preparations. They recommended that where 2 medicines in the same class are appropriate, the option with the lowest acquisition costs should be selected [1].

GLP-1 receptor agonists differ in their duration of action: short-acting (exenatide and lixisenatide), long-acting (dulaglutide, liraglutide, albiglutide). There are very few published head to head studies comparing GLP-1s, so network meta-analysis is most appropriate way to compare GLP-1s. A mixed treatment comparison (Network) meta-analysis finds that all GLP-1 RAs improve glycaemic control, reduce body weight and increase the risk of adverse gastrointestinal symtoms compared with placebo. No differences were found when short acting GLP-1 RAs were compared with each other, or when long acting GLP-1 RAs were compared with each other, dulaglutide, liraglutide and once weekly exenatide were superior to twice daily exenatide and lixisenatide at improving glycaemic control. Albiglutide and lixisenatide achieved smaller reductions in body weight than dulaglutide, liraglutide and exenatide [2].

Cardiovascular (CV) outcome data
Two trials (LEADER and ELIXA) have been published, evaluating the effect of GLP-1 RAs on rates of cardiovascular (CV) events:

- The LEADER trial reported liraglutide was superior to placebo for the composite outcome of first occurrence of death from CV causes, non-fatal MI, or non-fatal stroke.[3]
- ELIXA trial reported non-inferiority of lixisenatide to placebo.[4]
- Results of CV outcomes studies with exenatide and dulaglutide are awaited.

Safety

GLP-1 RAs may be associated with gastrointestinal adverse events (nausea, vomiting and diarrhoea).

Mixed treatment comparison meta-analysis found that all GLP-1 RAs increase risk of gastrointestinal side effects, however risk of diarrhoea is lower with lixisenatide than other GLP-1s, and risk of nausea and vomiting is lower with albiglutide, weekly exenatide and lixisenatide [2].

Acute pancreatitis is listed as a potential risk in the Summary of Product Characteristics (SPC). Patients should be alerted to characteristic symptoms: sudden severe pain in centre of abdomen, nausea and vomiting, diarrhoea, fever, jaundice

The incidence of hypoglycaemic episodes is low, and not found to be significantly different in GLP-1 comparisons [2].

Renal impairement:
Exenatide (prolonged release) not recommended in moderate impairment. Exenatide (daily), lixisenatide, dulaglutide and albiglutide are not recommended in severe renal impairment. No dose adjustment is required with liraglutide in mild, moderate and severe renal impairment [5]

See individual SPCs for further information on contraindications/interactions/side effects

Patient / Other factors	Cost (28 day cost – BNF)	

• Only available as a subcutaneous injection.
• Frequency of administration:
  ○ Albiglutide once weekly on the same day
  ○ Dulaglutide once weekly
  ○ Exenatide (Bydureon) once weekly.
  ○ Liraglutide once daily at any time independent of meals.
  ○ Lixisenatide once daily, within 1 hour before the first meal of the day or the evening meal.
  ○ Exenatide (Byetta) twice daily, within 1 hour before two main meals (at least 6 hours apart).
• There may be patient preference as to the ease of use of the different pen delivery devices.
	Albiglutide 30– 50mg once weekly
	Dulaglutide 1.5mg once weekly
	Exenatide 5-10 micrograms twice daily
	Exenatide 2mg once weekly
	Liraglutide 1.2-1.8mg once daily
	Lixisenatide 10-20 micrograms once daily
		£ 71.00
		£ 73.25
		£ 81.89
		£ 73.36
		£ 78.48 - £ 117.72
		£ 57.93

See accompanying document : PCN – Comparison of the commonly prescribed antidiabetic treatments for further detail on licensed combinations and use in renal and hepatic impairment

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