Sodium-glucose co-transporter 2 (SGLT-2) inhibitors: licensing, evidence, safety and cost comparison

For full details refer to Summary of Product Characteristics (SPC) at www.medicines.org.uk

Notes

a - Serious and life-threatening cases of diabetic ketoacidosis (DKA) have been reported in people taking SGLT-2 inhibitors (canagliflozin, dapagliflozin or empagliflozin) or shortly after stopping the SGLT-2 inhibitor. MHRA guidance (2015) advises testing for raised ketones in people with symptoms of diabetic ketoacidosis, even if plasma glucose levels are near normal (MHRA: April 2016 https://www.gov.uk/drug-safety-update/sglt2-inhibitors-updated-advice-on-the-risk-of-diabetic-ketoacidosis)

b – The FDA has strengthened the existing warning about the risk of acute kidney injury (AKI) for canagliflozin and dapagliflozin and to consider the risk of AKI prior to starting therapy. http://www.fda.gov/Drugs/DrugSafety/ucm505860.htm.

LEGEND: SU = sulfonylurea M = metformin P = pioglitazone I = insulin		Dapagliflozin▼ [Forxiga®]	Canagliflozin▼ [Invokana®]	Empaglifozin▼ [Jardiance®]
Specialist Drugs List Status		Specialist Advised (SA)	Specialist Advised (SA)	Specialist Advised (SA)
Daily cost/28 days (Drug tariff December 2016)		£1.31	£1.31	£1.31
Dose		10 mg daily	100 - 300 mg daily	10 -25 mg daily
Monotherapy		Yes	Yes	Yes
Dual therapy	With Metformin	Yes	Yes	Yes
	With SU	Yes	Yes	Yes
	With Pioglitazone	No	Yes	Yes
	With insulin	Yes	Yes	Yes
Triple therapy	With metformin and SU	Yes	Yes	Yes
	With metformin and pioglitazone	No	Yes	Yes
	With metformin and insulin	Yes	Yes	Yes

Renal impairment (Refer to Note b for risk of AK) above)	Mild	No dosage adjustment	No dosage adjustment	No dosage adjustment
	Moderate	Not recommended If renal function falls below CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m^2, dapagliflozin treatment should be discontinued	Should not be initiated Reduce dose to 100mg daily in patients tolerating canagliflozin whose eGFR falls persistently below 60 mL/min/1.73 m^2 or CrCl 60 mL/min, the dose of canagliflozin should be adjusted to or maintained at 100 mg once daily. Canagliflozin should be discontinued when eGFR is persistently below 45 mL/min/1.73 m^2 or CrCl persistently below 45 mL/min	Should not be initiated Reduce dose to 10mg in patients tolerating empagliflozin whose eGFR falls persistently below 60 ml/min/1.73 m^2 or CrCl below 60 ml/min. Empagliflozin should be discontinued when eGFR is persistently below 45 mL/min/1.73 m^2 or CrCl persistently below 45 mL/min
	Severe or End Stage Renal Disease	Not recommended	Not recommended	Not recommended
Hepatic impairment	Mild	No dosage adjustment	No dosage adjustment	No dosage adjustment
	Moderate	No dosage adjustment	No dosage adjustment	No dosage adjustment
	Severe	Starting dose of 5mg	Not recommended	Not recommended
Elderly		Over 65 years** - no dosage adjustment Over 75 years** - not recommended **Note increased risk of volume depletion in this population	Over 65 years** - no dosage adjustment Over 75 years** - no dosage adjustment **Note increased risk of volume depletion in this population	Over 65 years - no dosage adjustment Over 75 years** - no dosage adjustment Over 85 years - not recommended **Note increased risk of volume depletion in this population
National Institute for Health and Care Excellence (NICE)		NICE TA 390 – monotherapy ^ NICE TA 288; NG 28 Dual therapy with metformin; Combination with insulin with or without antidiabetic drugs NICE TA 418 Triple therapy with metformin and sulfonylurea	NICE TA 390 – monotherapy ^ NICE TA 315; NG 28 Dual therapy with metformin; Triple therapy in combination with M+ SU or M+ P; Combination with insulin with or without antidiabetic drugs	NICE TA 390 – monotherapy ^ NICE TA 336; NG 28 Dual therapy with metformin; Triple therapy in combination with M + SU or M + P ; Combination with insulin with or without antidiabetic drugs

Evidence (See NICE TAs) (inc only those trials published in full and linked to sources)	Dual therapy - 3 RCTs (+M +SU) (24 weeks, 52 weeks) Insulin - 2 RCT (12, 24 weeks)	Dual therapy - 2 RCTs (+M) (104 weeks, 52 weeks) Triple therapy - 3 RCTs (+M and SU/P) (52 weeks) Insulin - 1 RCT sub study (18 weeks)	Dual therapy - 4 RCTs (+P, metformin sub studies only) (24 weeks - 2 years) Triple therapy - 3 RCTs (M+ SU (sub study) and M+ P) (24 weeks - 76 weeks) Insulin - 2 RCTs (52-78 weeks) Renal impairment - 1RCT (24 weeks - 1 year)
CVD Outcomes Data	In terms of cardiovascular safety, a meta-analysis of 14 randomised controlled trials did not find any evidence that dapagliflozin is associated with increased cardiovascular risk for a composite end point of cardiovascular death, myocardial infarction and stroke (hazard ratio [HR] 0.79, 95% CI 0.54 to 1.17). (Ref - NICE TA 288)	CANVAS will report in 2017	EMPA-REGOUTCOME™ trial
Head to Head studies	No	No	No
Safety	Higher incidence of genital and urinary tract infections and a slightly higher incidence of volume depletion events (hypotension, hypovolaemia or dehydration) compared with placebo. Rates of bladder cancer (0.16% versus 0.03%), prostate cancer (0.34% versus 0.16%) and breast cancer (0.40% versus 0.22%) were higher in patients treated with dapagliflozin than in those treated with placebo respectively. (Ref - NICE TA 288)	The incidence of genital mycotic infection adverse events in women was higher in those receiving canagliflozin 100 mg (14.7%) and canagliflozin 300 mg (13.9%) than in those taking placebo (3.1%). In men, the incidence was 7.3% in the canagliflozin 100 mg group and 9.3% in the canagliflozin 300 mg groups, compared with 1.6% of men in the non‑canagliflozin group. (Ref - NICE TA 315)	Data showed that treatment with empagliflozin did not lead to an increase in hypoglycaemic events, except when empagliflozin was administered with a sulfonylurea or with insulin as background therapy. Across all trials, genital infections (generally of mild to moderate intensity) were consistently more frequent in the empagliflozin groups than with placebo. Incidence of urinary tract infections was similar across both empagliflozin groups and placebo, although it was reported that empagliflozin was associated with a greater frequency in women compared with placebo. Both genital and urinary tract infections were more common in women than men. Frequency of volume depletion was low across all

			clinical studies and comparable between all treatment groups. Fracture rates were very low and similar for all treatment groups across all empagliflozin trials. (Ref - NICE TA 336)

^Monotherapy in whom metformin is contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control, only if: a dipeptidyl peptidase‑4 (DPP‑4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.