Hertfordshire and West Essex Integrated Care System

NHS Hertfordshire and West Essex Integrated Care Board

Sodium-glucose cotransporter-2 (SGLT2) inhibitors (Gliflozins) in Adults with Type 2 Diabetes (T2DM)

- There are currently four SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin and ertugliflozin) licensed in the UK for the management of adults with T2DM.
- No head to head trials between the SGLT2 inhibitors have been conducted.
- Prescribing of SGLT-2 inhibitors to be in line with NICE NG28 and relevant NICE TAs. See table below for further details.
- Cardiovascular outcome data should be considered when making a decision on choice of SGLT-2 inhibitor. If patients and their clinicians consider ertugliflozin to be 1 of a range of equally suitable treatments, including canagliflozin, dapagliflozin and empagliflozin, the least expensive should be chosen.
- Dapagliflozin, canagliflozin and empagliflozin in combination with insulin with or without other antidiabetic drugs should only be initiated by community or secondary care specialists or by GPs with expertise in the treatment of patients with T2DM with insulin.
- Saxagliptin/Dapagliflozin (QTERN®) for the treatment of T2DM in adults is NOT RECOMMENDED for prescribing in primary or secondary care (DOUBLE RED)

Comparative data for SGLT-2 inhibitors

	28 day cost for standard daily doses	28 day cost for increased daily doses	Monotherapy	With Insulin (+/- MET)		Dual therapy	Triple therapy	Hepatic Impairment	Renal impairment (eGFR ml/min/1.73m^2)		
			License and NICE TA	License	NICE	License and NICE	License and NICE		**≥60 MILD**	**≥45 <60 MODERATE**	**<45 SEVERE**
Dapagliflozin	10mg daily £36.59	-	✓[1] NICE TA390	✓[2]	✓ NICE TA288	✓ (with MET)[3] NICE TA288	✓ (with MET & SU) NICE TA418	Mild/moderate – 10mg daily Severe – start at 5mg daily, titrate to 10mg if tolerated	No dose adjustment needed	**New patients** – No dose adjustment needed **Existing Patients** can continue without dose adjustment	**New patients** –If <15 then not recommended. **New and Existing Patients** consider additional antidiabetic drugs as reduced efficacy.
Canagliflozin	100mg daily £36.59 (£39.20 for 30 tablet pack)	300mg daily[4,5] £36.59 (£39.20 for 30 tablet pack)	✓[1] NICE TA390	✓[2]	✓ NICE TA315	✓ (with MET)[3] NICE TA315	✓ (with MET & SU or MET & PIO) NICE TA315	Mild/moderate - No dose adjustment Severe – not recommended	[6]No dose adjustment needed	**New patients** – Initiate with 100mg **Existing patients** – Continue 100 mg.	**New patients** – Initiate with 100mg. If <30 then it should not be initiated. **Existing Patients** - Continue 100 mg daily.
Empagliflozin	10mg daily[7] £36.59	25mg daily[4] £36.59	✓[1] NICE TA390	✓[2]	✓ NICE TA336	✓ (with MET)[3] NICE TA336	✓ (with MET & SU or MET & PIO) NICE TA336	Mild/moderate - No dose adjustment Severe – not recommended	[6]No dose adjustment needed	**New patients** – Not recommended. **Existing patients** – Adjust/maintain dose at 10mg OD	**New patients** – Not recommended. **Existing Patients** - discontinue.

Ertugliflozin ▼	5mg daily £29.40	15mg daily £29.40[8,9]	✓[1] NICE TA572	✓[2]	Not stated	✓ (with MET)[3] NICE TA572	✓ (with MET & DPP-4)[10] NICE TA583	Mild/moderate - No dose adjustment Severe – not recommended	[11]No dose adjustment needed	**New patients** - Not recommended. **Existing Patients** can continue without dose adjustment	**New patients** - Not recommended. **Existing Patients** - discontinue.

MET= metformin; SU= sulphonylurea; PIO=pioglitazone DPP-4 = dipeptidyl peptidase inhibitor

1= Where MET is inappropriate and only if a DPP-4 inhibitor (gliptin) would otherwise be prescribed and a SU or PIO is not appropriate.

2=when used in combination with insulin or an insulin secretagogue, a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycaemia.

3= In combination with metformin only if SU contraindicated or not tolerated or if there is significant risk of hypoglycaemia

4=Where standard daily dose is tolerated and 'tighter glycaemic control is needed' and eGFR ≥ 60 ml/min.

5=Care should be taken when increasing the dose in patients ≥ 75 years of age, patients with known cardiovascular disease, or other patients for whom the initial canagliflozin-induced diuresis poses a risk. In patients with evidence of volume depletion, correcting this condition prior to initiation of canagliflozin is recommended.

6= Monitor renal function before initiating and at least annually. Thereafter, prior to concomitant medical products that may reduce renal function.

7= in patients 75 years old and older, an increased risk for volume depletion should be considered. In patients aged 85 years and older, initiation is not recommended due to limited therapeutic experience.

8= In patients who tolerate 5mg and additional glycaemic control is required the dose can be increased to 15mg

9= In patients with volume depletion, correcting this condition prior to initiation is recommended. Limited experience in patients older than 75 years.

10= In triple therapy with MET and a DPP-4 only if the disease is not controlled and a SU or PIO is not appropriate.

11= Monitor renal function before initiating and periodically during treatment. More frequently in patients with an eGFR < 60 ml/min.

Common side effects

Canagliflozin

- Balanoposthitis; constipation; dyslipidaemia; hypoglycaemia (in combination with insulin or sulfonylurea); increased risk of infection; nausea; thirst; urinary disorders; urosepsis

Dapagliflozin

- Back pain; balanoposthitis; diabetic ketoacidosis (discontinue immediately); dizziness; dyslipidaemia; hypoglycaemia (in combination with insulin or sulfonylurea); increased risk of infection; rash; urinary disorders

Empagliflozin

- Balanoposthitis; hypoglycaemia (in combination with insulin or sulfonylurea); increased risk of infection; skin reactions; thirst; urinary disorders; urosepsis

Ertugliflozin ▼

- Vulvovaginal mycotic infection and other female genital mycotic infections; balanitis candida and other male genital mycotic infections; hypoglycaemia (in combination with insulin or sulfonylurea); hypovolaemia; increased risk of infection; polydipsia; thirst; urinary disorders; vulvovaginal pruritus;

Drug Interactions

All SGLT-2 inhibitors (Canagliflozin, Dapagliflozin, Empagliflozin and Ertugliflozin)

- Effect of diuretics may be increased. Increased risk of dehydration and hypotension.
- Hypoglycaemic effects of insulin and insulin secretagogues, such as sulphonylureas may be enhanced

Canagliflozin

- Plasma digoxin concentrations may increase. No dose adjustment of digoxin is recommended but patients at risk should be monitored for digoxin toxicity.
- Enzyme inducers such as St. John's wort [*Hypericum perforatum*], rifampicin, barbiturates, phenytoin, carbamazepine, ritonavir and efavirenz may decrease canagliflozin concentrations and may lead to decreased efficacy.
- Cholestyramine may decrease canagliflozin absorption. Administer canagliflozin 1 hour before or 4 hours after cholestyramine.

Empagliflozin

- Co-medication with known inducers of UGT enzymes (such as St. John's wort [*Hypericum perforatum*], barbiturates, phenytoin, carbamazepine, ritonavir, efavirenz) should be avoided due to a potential risk of decreased efficacy.

MHRA Drug Safety Update

- MHRA Drug Safety update April 2016: SGLT-2 inhibitors: updated advice on the management of the risk of diabetic ketoacidosis. https://www.gov.uk/drug-safety-update/sglt2-inhibitors-updated-advice-on-the-risk-of-diabetic-ketoacidosis
- MHRA Drug Safety update March 2017: Canagliflozin (Invokana, Vokanamet): increased risk of lower-limb amputation (mainly toes) in patients with type 2 diabetes. https://www.gov.uk/drug-safety-update/sglt2-inhibitors-updated-advice-on-increased-risk-of-lower-limb-amputation-mainly-toes
- MHRA Drug Safety update February 2019: SGLT2 inhibitors: reports of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum). https://www.gov.uk/drug-safety-update/sglt2-inhibitors-reports-of-fournier-s-gangrene-necrotising-fasciitis-of-the-genitalia-or-perineum
- MHRA Drug safety update March 2020: SGLT2 inhibitors: monitor ketones in blood during treatment interruption for surgical procedures or acute serious medical illness. https://www.gov.uk/drug-safety-update/sglt2-inhibitors-monitor-ketones-in-blood-during-treatment-interruption-for-surgical-procedures-or-acute-serious-medical-illness

Cardiovascular Outcome Trial (CVOT) Data from RCTs

- Empagliflozin: **EMPA-REG Outcomes study**. Secondary prevention population. Primary endpoint: 3 point MACE (major adverse cardiovascular events) showed a relative risk reduction of 14% compared to placebo. Mean observation time in the study was 3.1 years.
- Canagliflozin: **CANVAS program**. 1/3 primary prevention and 2/3 secondary prevention population. Primary endpoint: 3 point MACE relative risk reduction of 14% compared to placebo. Mean duration of follow up in the study was 188.2 weeks.
- Dapagliflozin: **DECLARE-TIMI58.** 60% primary prevention and 40 % secondary prevention population. Primary endpoints: (1) 3 point MACE not significantly reduced compared to placebo, (2) Hospitalization for heart failure or cardiovascular death relative risk reduction of 17% compared to placebo. Median follow up in the study was 4.2 years.
- Ertugliflozin: **VERTIS-CV.** Primary endpoint: Showed non-inferiority for 3 point MACE compared with placebo. Secondary key endpoints were not met (outcome of CV death/hospitalisation for heart failure, CV death and renal composite. Patients were followed for a mean of 3.5 years. Major adverse cardiac event reductions were not statistically significant for Ertugliflozin.

References

- Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin Summary of Product Characteristics available at www.medicines.org.uk
- NICE BNF at https://bnf.nice.org.uk/ Last updated: November 2019
- Drug Tariff- November 2019 https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff
- NICE TA 390. Canagliflozin, Dapagliflozin and Empagliflozin as monotherapies for treating type 2 diabetes. May 2016. https://www.nice.org.uk/guidance/ta390
- NICE TA 572. Ertugliflozin as monotherapy or with metformin for treating type 2 diabetes. March 2019. https://www.nice.org.uk/guidance/ta572
- NICE TA 288. Dapagliflozin in combination therapy for treating type 2 diabetes. June 2013. https://www.nice.org.uk/Guidance/TA288
- NICE TA 418 Dapaglifozin in triple therapy for type 2 diabetes. November 2016. https://www.nice.org.uk/guidance/ta418
- NICE TA 315 Canagliflozin in combination therapy for treating type 2 diabetes. June 2014. http://www.nice.org.uk/guidance/TA315
- NICE TA 336 Empagliflozin in combination therapy for treating type 2 diabetes March 2015. https://www.nice.org.uk/guidance/ta336/chapter/1-Guidance
- 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 TA679**:** Dapagliflozin for treating chronic heart failure with reduced ejection fraction, February 2021. Available at http://www.nice.org.uk/guidance/TA679
- EMPA-REG OUTCOME- Zinman, B., Inzucchi, S., Lachin, J., Wanner, C., Ferrari, R., Fitchett, D., Bluhmki, E., Hantel, S., Kempthorne-Rawson, J., Newman, J., Johansen, O., Woerle, H. and Broedl, U. (2014). Empagliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients (EMPA-REG OUTCOME™). New England Journal of Medicine (2015) https://www.nejm.org/doi/full/10.1056/NEJMoa1504720
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- Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. New England Journal of Medicine (2019) . [online] Available at: https://www.nejm.org/doi/full/10.1056/NEJMoa1812389
- Ertugliflozin and cardiovascular outcomes in patients with type 2 diabetes. VERTIS-CV. Cannon CP, et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. N Engl J Med. 2020; 383(15):1425-1435 https://www.nejm.org/doi/full/10.1056/NEJMoa2004967

Version	1.2 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:	The 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	1.1 Harmonisation of Hertfordshire Medicines Management Committee (HMMC) guidance and West Essex Medicines Optimisation Programme Board (WEMOPB) guidance updates include: • Rebadging with HWE ICB and removal of ENHCCG and HVCCG headers • Review date removed and replaced with standard statement.