NHS East and North Hertfordshire Clinical Commissioning Group

NHS Herts Valleys Clinical Commissioning Group

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.
- As at December 2019, clinical outcome data is available for three of the four SGLT2 inhibitors around their cardiovascular effects in people with T2DM. Ertugliflozin is still to report on this data.
- This document summarises the key prescribing considerations.

NICE Technology Appraisal Recommendation

NICE makes recommendations for when SGLT2 inhibitors can be considered in adults with T2DM; Hertfordshire Medicines Management Committee Recommendations are in line with NICE guidance:

Monotherapy

NICE TA 390: Canagliflozin, Dapagliflozin and Empagliflozin and NICE TA 572: Ertugliflozin as monotherapies for treating T2DM

Monotherapy recommended as option in adults for whom metformin is contraindicated or not tolerated and when diet & exercise alone do not provide adequate glycaemic control, only if:

- a DPP-4 inhibitor would otherwise be prescribed and
- a sulfonylurea or pioglitazone is not appropriate.

Dual therapy

NICE TA 315: Canagliflozin, NICE TA288: Dapagliflozin, TA 336: Empagliflozin, TA 572: Ertugliflozin as combination therapies for treating T2DM

In a dual therapy regimen in combination with metformin is recommended as an option, only if:

- a sulfonylurea is contraindicated or not tolerated or
- the person is at significant risk of hypoglycaemia or its consequences.

In combination with insulin

NICE TA 315: Canagliflozin, NICE TA288: Dapagliflozin, TA 336: Empagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option.

Triple therapy

Canagliflozin/Empagliflozin: In a triple therapy regimen it is recommended as an option in combination with metformin and a sulfonylurea or metformin and pioglitazone.

Dapagliflozin: In a triple therapy regimen it is recommended as an option only in combination with metformin and a sulfonylurea.

Ertugliflozin: In a triple therapy regime as an option with metformin and a dipeptidyl peptidase (DPP-4) inhibitor only if the disease is uncontrolled with metformin and a DPP-4 inhibitor and a sulfonylurea or pioglitazone is not appropriate

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

SGLT2 inhibitor therapy should only be continued if the person has a reduction of at least 5.5mmol/mol (0.5%) in HbA1c in 6 months

Saxagliptin/Dapagliflozin (QTERN®) for the treatment of T2DM in adults is NOT RECOMMENDED for prescribing in primary or secondary care (DOUBLE RED)

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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	NICE	License and NICE	License	NICE	License	NICE		**≥60 MILD**	**≥45 <60 MODERATE**	**<45 SEVERE**
Dapagliflozin	10mg daily[4] £36.59	-	√[2]	√[5]	√	√	√(with MET)[6]	√ (exclude PIO)[3]	√(with MET & SU)	Mild/moderate – 10mg daily Severe – start at 5mg daily, titrate to 10mg if tolerated	No dose adjustment needed	**New patients** - Not recommended. **Existing Patients** can continue without dose adjustment	**New patients** - Not recommended. **Existing Patients** - discontinue.
Canagliflozin	100mg daily £36.59 (£39.20 for 30 tablet pack)	300mg daily[1] £36.59 (£39.20 for 30 tablet pack)	√[2]	√[5]	√	√	√(with MET)[6]	√	√ (with MET & SU or PIO)	Mild/moderate - No dose adjustment Severe – not recommended	No dose adjustment needed	**New patients** – Not recommended **Existing patients** – Adjust/ maintain dose at 100mg daily.	**New patients** – Not recommended **Existing Patients** - discontinue.
Empagliflozin	10mg daily £36.59	25mg daily[1] £36.59	√[2]	√[5]	√	√	√(with MET)[6]	√	√(with MET & SU or PIO)	Mild/moderate - No dose adjustment Severe – not recommended	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[7]	√[2]	√[5]	√	√	√(with MET)[6]	√	√(with MET & DPP-4)[8]	Mild/moderate - No dose adjustment Severe – not recommended	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 standard daily dose is tolerated and 'tighter glycaemic control is needed' and eGFR ≥ 60 ml/min

2=where MET is inappropriate.

3=not recommended for use in patients concomitantly treated with pioglitazone (precautionary measure as a result of concerns about bladder cancer rates for both drugs).

4=Dapagliflozin is not recommended in patients >75 years

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

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

7= Starting dose 5mg. In patients who tolerate 5mg and additional glycaemic control is required increase to 15mg

8= In triple therapy with a DPP-4 only when a SU or PIO is not appropriate.

This HMMC recommendation is based upon the evidence available at the time of publication. The recommendation will be reviewed upon request in the light of new evidence becoming available.

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.

NB: This list is not exhaustive; please refer to BNF/SPC for further information http://www.medicines.org.uk/emc/

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; 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; pruritus generalised; thirst; urinary disorders

Ertugliflozin

- Vulvovaginal mycotic infection and other female genital mycotic infections; balanitis candida and other male genital mycotic infections; hypoglycaemia; volume depletion; increased urination; vulvovaginal pruritus; thirst

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 June 2016: Canagliflozin (Invokana▼, Vokanamet▼): signal of increased risk of lower extremity amputations observed in trial in high cardiovascular risk patients. https://www.gov.uk/drug-safety-update/canagliflozin-invokana-vokanamet-signal-of-increased-risk-of-lower-extremity-amputations-observed-in-trial-in-high-cardiovascular-risk-patients
- 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

Additional Safety Concerns highlighted by US FDA Safety Review

- Drug Safety Communications August 2018: FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes https://www.fda.gov/Drugs/DrugSafety/ucm617360.htm
- Drug Safety Communications June 2016: FDA strengthens kidney warnings for diabetes medicines Canagliflozin (Invokana, Invokamet) and Dapagliflozin (Farxiga, Xigduo XR) https://www.fda.gov/Drugs/DrugSafety/ucm505860.htm
- Drug Safety Communications December 2015: Revises labels of SGLT2 inhibitors for diabetes to include warnings about serious urinary tract infections. https://www.fda.gov/Drugs/DrugSafety/ucm475463.htm

Cost of 1 month supply of metformin with SGLT2 inhibitors (combination products)

Combination products with a fixed dose of metformin are available for Empagliflozin, Canagliflozin and Dapagliflozin. The cost of the combination product in all cases is the same as the cost of the SGLT2 inhibitor by itself.

Cardiovascular Outcome Trial (CVOT) Data from RCTs

- RCTs for the cardiovascular outcomes for three SGLT2 inhibitors are available:
  - 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. 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.
- RCT for cardiovascular outcomes for Ertugliflozin are currently on-going. This paper will be updated once the RCT is published.

References

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- 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
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- NICE TA 336 Empagliflozin in combination therapy for treating type 2 diabetes | Guidance | NICE. [online] Available at: 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
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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