East and North Hertfordshire Clinical Commissioning Group

Herts Valleys Clinical Commissioning Group

HERTFORDSHIRE MEDICINES MANAGEMENT COMMITTEE (HMMC)
NICE TECHNOLOGY APPRAISALS – RECOMMENDED

NICE TAs 315 & 390 – Canagliflozin for treating type 2 diabetes (T2DM)
RECOMMENDED FOR RESTRICTED USE

Name: generic (trade)	What it is	Indication	Date decision last revised	Decision status	NICE / SMC Guidance
Canagliflozin (Invokana®)	Sodium-glucose co-transporter 2 inhibitor	Treatment of type 2 diabetes (T2DM)	September 2016 (update of July 2015)	Final	NICE TAs 315 390– recommended SMC - recommended

HMMC Recommendation, in line with NICE technology appraisal guidance 315 and 390:

RECOMMENDED FOR RESTRICTED USE AS AN OPTION FOR TREATING T2DM:

Monotherapy:

- Canagliflozin, as monotherapy is recommended as an option for treating type 2 diabetes in adults for 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.

Only continue if the person has had a reduction of at least 5.5mmol/mol (0.5%) in HbAlc in 6 months.
Initiation can be undertaken by primary, community or secondary care.

- **In a dual therapy regimen** in combination with metformin (as an alternative to pioglitazone and DPP4 inhibitors [gliptins]):
  - Instead of a sulfonylurea as second line therapy to first line metformin when control of blood glucose remains or becomes inadequate (HbA1c ≥48mmol/mol [6.5%]), or higher level agreed with patient if:
    - The person is at significant risk of hypoglycaemia or its consequences (for example, older people and people in certain jobs [e.g. those working at heights or with heavy machinery] or people in certain social circumstances [for example, those living alone]) OR
    - The person does not tolerate a sulfonylurea or a sulfonylurea is contraindicated.
  - Only continue if the person has had a reduction of at least 5.5mmol/mol (0.5%) in HbAlc in 6 months.
  - Initiation can be undertaken by primary, community or secondary care.

- **in combination with insulin** with or without other antidiabetic drugs (metformin +/- sulfonylurea):
  - only continue if the person has had a reduction of at least 5.5 mmol/mol (0.5%) in HbA1c in 6 months.
  - initiation should be undertaken by community or secondary care specialists or by GPs with expertise in the treatment of patients with T2DM with insulin.

- **in a triple therapy regimen** in combination with metformin and a sulfonylurea **or** metformin and a thiazolidinedione.
  - only continue if the person has had a reduction of at least 5.5 mmol/mol (0.5%) in HbA1c in 6 months.
  - initiation should be undertaken by community or secondary care specialists or by GPs where appropriate

Further recommendation, following consultation with local specialists:
The recommendations concerning the 300mg dose:

- **Dose increase from 100mg to 300mg canagliflozin is only recommended if individualised Hba1c target not reached.**

Produced by Hertfordshire Pharmacy and Medicines Optimisation Teams
East and North Herts CCG and NHS Herts Valleys CCG
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.

- **Review dose increase after 6 months and decrease to 100mg or discontinue if HbA1c reduction is less than 5.5 mmol/mol (0.5%).**
- **Dose increase to 300mg canagliflozin can be undertaken in any care setting based on improvement in Hba1c without target attainment as stated above.**

Background information, costs, monitoring, contra-indications and adverse events

- **Costs – The SGLT2 inhibitors, canagliflozin, dapagliflozin and empagliflozin are currently the highest cost oral antidiabetic drugs (excluding tolbutamide which is rarely used).**
- Canagliflozin is now licensed and recommended by NICE as monotherapy, dual therapy and triple therapy.
- Canagliflozin is usually given at a dose of 100 mg once daily, preferably before the first meal of the day.

Renal function

- **The efficacy of canagliflozin is dependent on renal function.** Refer to table for dosage information:

Usual dose	100mg od
Where 100mg daily is tolerated and 'tighter glycaemic control is needed' and eGFR ≥ 60 mL/min/1.73 m^2 or CrCl ≥ 60 mL/min	300mg od(see notes on page 1)
New patients with eGFR < 60 mL/min/1.73 m^2 or CrCl < 60 mL/min	contraindicated
Existing patients whose eGFR falls persistently below 60 mL/min/1.73 m^2 or CrCl <60 mL/min	Adjust or maintain dose at 100mg od
Existing patients when eGFR is persistently below 45 mL/min/1.73 m^2 or CrCl persistently below 45 mL/min	discontinue

- **Monitoring of renal function is recommended as follows**:
  - Prior to initiation of canagliflozin and at least annually thereafter
  - Prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter.
  - For renal function approaching moderate renal impairment, at least twice to 4 times per year. If renal function falls persistently below eGFR 45 mL/min/1.73 m^2 or CrCl < 45 mL/min, canagliflozin treatment should be discontinued.
- Elderly patients (≥ 65 years old) may be at a greater risk for volume depletion, are more likely to be treated with diuretics, and to have impaired renal function. In patients ≥ 75 years of age, a higher incidence of adverse reactions associated with volume depletion (e.g., postural dizziness, orthostatic hypotension, hypotension) has been reported. In addition, in such patients greater decreases in eGFR were reported.
- **Common adverse reactions**: include urinary tract and genital infections, constipation, thirst, nausea and dyslipidaemia.
- There is an increased risk of hypoglycaemia when combined with insulin or sulfonylureas.
- There is currently no cardiovascular safety outcome data for dapagliflozin and canagliflozin.
- Canagliflozin has not been studied in combination with glucagon-like peptide 1 (GLP-1) analogues or DPP4 inhibitors (gliptins).
- **MHRA Drug Safety update June 2015** reports that serious and life-threatening cases of diabetic ketoacidosis have been reported in patients taking sodium-glucose co-transporter 2 (SGLT2) inhibitors (canagliflozin, dapagliflozin or empagliflozin). It advises to test for raised ketones in patients with acidosis symptoms, even if plasma glucose levels are near-normal,
- **MHRA Drug Safety Update April 2016** on DKA instructs:
  - not to restart treatment with any SGLT2 inhibitor in patients who experienced DKA during use, unless another cause for DKA was identified and resolved
  - interrupt treatment with the SGLT2 inhibitor in patients who are hospitalised for major surgery or acute serious illnesses; treatment may be restarted once the patient's condition has stabilised

  MHRA LINK
- **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. MHRA JUNE 2016 LINK

Reference:

- NICE TA 315 – Canagliflozin in combination therapy for treating type 2 diabetes (T2DM), July 2014 NICETA315
- NICE TA 390 – Canagliflozin in monotherapy for treating type 2 diabetes (T2DM), May 2016 NICE TA390
- Refer to Summary of Product Characteristics for further information on canagliflozin http://www.medicines.org.uk/emc/
- MHRA Drug Safety Update MHRA Drug Safety June_2015

Produced by Hertfordshire Pharmacy and Medicines Optimisation Teams
East and North Herts CCG and NHS Herts Valleys CCG