PAN MERSEY APC

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NHS Pan Mersey Area Prescribing Committee

CANAGLIFLOZIN, DAPAGLIFLOZIN and EMPAGLIFLOZIN as COMBINATION THERAPIES : a multiple prescribing statement

GREEN

The Pan Mersey Area Prescribing Committee recommends the prescribing of CANAGLIFLOZIN, DAPAGLIFLOZIN and EMPAGLIFLOZIN as combination therapies for the treatment of type 2 diabetes in accordance with NICE guidance

Canagliflozin, dapagliflozin and empagliflozin are selective sodium-glucose cotransporter-2 (SGLT-2) inhibitors

NICE technology appraisals TA 315[1] (canagliflozin), TA288[2] and TA418[3] (dapagliflozin) and TA336[4] (empagliflozin) recommend SGLT-2 inhibitors as add-on COMBINATION THERAPIES (dual and triple regimens) as an option for treating type 2 diabetes in adults.

- **in a dual therapy regimen in combination with metformin only if:**
  - a sulfonylurea is contraindicated or not tolerated or
  - the person is at significant risk of hypoglycaemia or its consequences (for example, older people or those in certain jobs e.g. working at heights or with heavy machinery or in certain social circumstances e.g. living alone)

- **in a triple therapy regimen in combination with metformin and a sulfonylurea**

- **in combination with insulin, with or without other antidiabetic drugs**

- **In addition, canagliflozin and empagliflozin are recommended in combination with metformin and pioglitazone**

NB: Dapagliflozin is NOT recommended for use in patients concomitantly treated with pioglitazone due to the potential for an increased risk of bladder cancer.[10]

Prescribers are reminded that the MHRA has issued advice in relation to SGLT-2 inhibitors:

- Risk of diabetes ketoacidosis (DKA) with SGLT-2 inhibitors MHRA Drug Safety Update[5]
- Canagliflozin may increase the risk of lower-limb amputation (mainly toes)-evidence does not show an increased risk with the other SGLT-2 inhibitors, but this risk may be a class effect MHRA Drug Safety Update[6]

See NICE Guideline 28 Type 2 diabetes in adults[7]: management algorithm for where a DPP-4 inhibitor would otherwise be prescribed

NB: the effectiveness of SGLT-2 inhibitors is dependent on adequate renal function; see the "Implementation Notes" for the individual drugs for further details.

For the current advice on SGLT-2 inhibitors as monotherapy see the Pan Mersey APC prescribing monotherapy statement

Note: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

CANAGLIFLOZIN film coated tablets (Invokana®▼) as COMBINATION THERAPY

EFFECTIVENESS[1]

Canagliflozin is a selective sodium-glucose cotransporter-2 (SGLT-2) inhibitor. It lowers blood glucose by blocking the reabsorption of glucose in the kidneys and promoting excretion of excess glucose in the urine.

As part of dual therapy in combination with metformin, canagliflozin provides broadly comparable glycaemic control to gliptins and dapagliflozin and may result in greater reductions in weight and blood pressure.

As part of triple therapy in combination with metformin and a sulfonylurea, canagliflozin gives a comparable HbA1c reduction compared with a gliptin and greater reductions in weight and blood pressure.

As an add-on treatment to insulin, canagliflozin is slightly more effective in reducing HbA1c and weight than gliptins and dapagliflozin.

SAFETY[5,6,8]

Contraindications: hypersensitivity to the active ingredients or any of the excipients, type 1 diabetes, treatment of diabetic ketoacidosis.

There is an increased rate of adverse reactions related to volume depletion (postural dizziness, orthostatic hypotension, hypotension) with the 300mg dose and in the first three months of treatment. Not recommended for use in patients receiving loop diuretics or with volume depletion (temporary interruption of treatment recommended for patients who develop volume depletion until it is corrected).

Urinary tract infections, mostly mild to moderate, more frequently reported compared to placebo. No increase in incidence of recurrent infections.

In subjects ≥ 75 years of age, a higher proportion had adverse reactions related to volume depletion.

Limited experience in heart failure NYHA class III, none in NYHA class IV.

Rare cases of DKA, including life-threatening cases, have been reported in patients treated with SGLT-2 inhibitors, including canagliflozin. See MHRA Drug Safety Update (April 2016)

The MHRA have issued an alert re an increased risk of lower extremity amputations observed in trial in high cardiovascular risk patients

See MHRA Updated Drug Safety Update (March 2017)

Consult the SPC for full information.

COST per patient per year

Costs taken from Dictionary of Medicines and Devices (dm+d)[9]

Canagliflozin:	£477
Dapagliflozin:	£477
Empagliflozin	£477
Sitagliptin	£434
Linagliptin	£434
Saxagliptin	£412

PATIENT FACTORS[8]

Efficacy is dependent on renal function and is reduced in moderate renal impairment and probably absent in severe renal impairment. Not recommended for use in patients with estimated glomerular filtration rate [eGFR] <45 ml/min/1.73m^2. Maximum dose of 100mg daily in patients with eGFR <60 ml/min/1.73m^2 No dosage adjustment for patients with eGFR ≥60 ml/min/1.73m^2

No dosage adjustment for mild or moderate hepatic impairment. Not recommended in severe hepatic impairment.

PRESCRIBING INFORMATION

The recommended starting dose is 100 mg once daily, preferably before the first meal of the day. Tablets should be swallowed whole. If tolerated and tighter glycaemic control is required, the dose can be increased to 300mg daily provided eGFR ≥ 60 ml/min/1.73 m$^{2.}$ Care should be taken when increasing the dose for patients ≥ 75 years, with cardiovascular disease or with other co-morbidities where the initial diuresis poses a risk. When canagliflozin is used in combination with insulin or an insulin secretagogue, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia.

IMPLEMENTATION NOTES

Renal function should be monitored prior to initiation of canagliflozin and at least yearly thereafter. Additional monitoring is recommended prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter.

For renal function approaching moderate renal impairment, monitoring is recommended at least 2 to 4 times per year. Discontinue canagliflozin if eGFR persistently < 45 ml/min/1.73 m$^{2.}$

DAPAGLIFLOZIN film coated tablets (Forxiga®▼) as COMBINATION THERAPY

EFFECTIVENESS[2,3]

Dapagliflozin is a selective and reversible inhibitor of renal sodium–glucose cotransporter-2 (SGLT-2), the major transporter responsible for renal glucose reabsorption. Plasma glucose is lowered by reducing renal glucose reabsorption, leading to increased urinary glucose excretion.

In clinical trials as an add-on to metformin, dapagliflozin has demonstrated a statistically significant reduction in HbA1c and body weight compared with placebo in two studies of 24 weeks. And as an add-on to insulin has demonstrated a statistically significant reduction in HbA1c, body weight and systolic blood pressure compared with placebo in one study of 12 weeks and one study of 24 weeks.

Clinical trials demonstrated that dapagliflozin in triple therapy is more effective than placebo in reducing HbA1c and weight. In comparison with the other SGLT-2 inhibitors and the DPP-4 inhibitors, network meta analyses demonstrated that dapagliflozin had a similar effect on HbA1c as the other SGLT-2 inhibitors and DPP-4 inhibitors, but that the SGLT-2 inhibitors produced more weight loss than the DPP-4 inhibitors. Clinical trials also suggested that dapagliflozin may have a sustained beneficial effect on blood pressure.

SAFETY[5,6,10]

Contraindications: hypersensitivity to the active substance or to any of the excipients, type 1 diabetes mellitus, treatment of diabetic ketoacidosis.

Dapagliflozin decreases blood pressure, which may be more pronounced in patients with very high blood glucose concentrations. Not recommended for use in patients receiving loop diuretics or with volume depletion, temporary interruption of treatment recommended for patients who develop volume depletion until it is corrected.

Urinary tract infections more frequently reported compared to placebo, consider temporary interruption of dapagliflozin when treating pyelonephritis or urosepsis.

In subjects ≥ 65 years of age, a higher proportion had adverse reactions related to renal impairment/failure and volume depletion.

Limited experience in NYHA class I-II, none in NYHA class III-IV.

Not recommended for use in patients concomitantly treated with pioglitazone.

Rare cases of DKA, including life-threatening cases, have been reported in patients treated with SGLT-2 inhibitors,. See MHRA Drug Safety Update (April 2016)

The MHRA have issued an alert re an increased risk of lower extremity amputations observed in trial in high cardiovascular risk patients

See MHRA Updated Drug Safety Update (March 2017)

See SPC for full details.

COST per patient per year

Costs taken from Dictionary of Medicines and Devices (dm+d)[9]

Canagliflozin:	£477
Dapagliflozin:	£477
Empagliflozin	£477
Sitagliptin	£434
Linagliptin	£434
Saxagliptin	£412

PATIENT FACTORS[10]

Efficacy is dependent on renal function and is reduced in moderate renal impairment and probably absent in severe renal impairment. Not recommended for use in patients with estimated glomerular filtration rate [eGFR] <60 ml/min/1.73m^2. No dosage adjustment for mild renal impairment.

No dosage adjustment for mild or moderate hepatic impairment. In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg.

PRESCRIBING INFORMATION

The recommended dose is 10 mg once daily at any time of day, with or without food. Tablets should be swallowed whole. When dapagliflozin is used in combination with insulin or an insulin secretagogue, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia. A starting dose of 5mg daily should be used in severe hepatic impairment. Therapeutic experience in patients 75 years and older is limited – initiation not recommended.

IMPLEMENTATION NOTES

Renal function should be monitored prior to initiation of dapagliflozin and at least yearly thereafter. Additional monitoring is recommended prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter.

For renal function approaching moderate renal impairment, monitoring is recommended at least 2 to 4 times per year. Discontinue dapagliflozin if CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m^2.

EMPAGLIFLOZIN film coated tablets (Jardiance®▼) as COMBINATION THERAPY

EFFECTIVENESS[4,12]

Empagliflozin lowers blood glucose by blocking the reabsorption of glucose in the kidneys and promoting excretion of excess glucose in the urine.

NICE concludes that on the basis of clinical trial results, empagliflozin in combination with other antidiabetic agents is proven to be an effective treatment compared with placebo.

NICE further concludes that on the basis of the network meta-analyses provided by the manufacturer, empagliflozin as part of dual therapy, triple therapy and as an add-on to insulin appears to provide comparable glycaemic control to both other SGLT-2 inhibitors and dipeptidylpeptidase-4 inhibitors.

EMPA-REG OUTCOME trial, showed that empagliflozin reduced the risk of CV death by 38 percent vs placebo in patients with T2D and established CV disease when added to standard of care and significantly reduced the risk of the primary endpoint of CV death, non-fatal heart attack or non-fatal stroke by 14 percent versus placebo There were no statistically significant differences in the risk of non-fatal heart attack or non-fatal stroke. [12]

SAFETY[5,6,11]

Contraindications: hypersensitivity to the active ingredients or any of the excipients, type 1 diabetes, treatment of diabetic ketoacidosis.

In case of conditions that may lead to fluid loss (e.g. gastrointestinal illness), careful monitoring of volume status and electrolytes is recommended for patients receiving empagliflozin. Temporary interruption of treatment with empagliflozin should be considered until the fluid loss is corrected.

In patients 75 years and older, an increased risk for volume depletion should be taken into account. Experience in New York Heart Association (NYHA) class I-II is limited, and there is no experience in clinical studies with empagliflozin in NYHA class III-IV.

Rare cases of DKA, including life-threatening cases, have been reported in patients treated with SGLT-2 inhibitors. MHRA Drug Safety Update (April 2016)

The MHRA have issued an alert re an increased risk of lower extremity amputations observed in trial in high cardiovascular risk patients

See MHRA Updated Drug Safety Update (March 2017)

Consult the SPC for full information.

COST per patient per year

Costs taken from Dictionary of Medicines and Devices (dm+d)[9]

Canagliflozin:	£477
Dapagliflozin:	£477
Empagliflozin	£477
Sitagliptin	£434
Linagliptin	£434
Saxagliptin	£412

PATIENT FACTORS[11]

Should not be initiated in patients with an eGFR below 60 ml/min/1.73 m2. In patients tolerating empagliflozin whose eGFR is persistently below 60 ml/min/1.73 m2, the dose should be adjusted to or maintained at 10 mg once daily. Empagliflozin should be discontinued when eGFR is persistently below 45 ml/min/1.73 m2 and should not be used in patients with ESRD or in patients on dialysis as it is not expected to be effective in these patients.

In patients aged 85 years and older, initiation of empagliflozin therapy is not recommended due to the limited therapeutic experience.

No dose adjustment is required for patients with hepatic impairment. Therapeutic experience in patients with severe hepatic impairment is limited and therefore not recommended for use in this population.

PRESCRIBING INFORMATION

The recommended starting dose is 10mg once daily. Tablets can be taken with or without food and should be swallowed whole with water. If tolerated and tighter glycaemic control is required, the dose can be increased to 25mg daily provided eGFR ≥ 60 ml/min/1.73 m2. Care should be taken when increasing the dose for patients ≥ 75 years, with cardiovascular disease or with other co-morbidities where the initial diuresis poses a risk. When empagliflozin is used in combination with insulin or an insulin secretagogue, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia.

IMPLEMENTATION NOTES

Renal function should be monitored prior to initiation of empagliflozin and at least yearly thereafter.

Additional monitoring is recommended prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter.

Empagliflozin should not be initiated in patients with an eGFR <60 ml/min/1.73m^2 and should be discontinued if eGFR persistently < 45 ml/min/1.73 m^2. Max dose for eGFR 45-60 ml/min/1.73m^2 is 10mg.

REFERENCES

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