



PAN MERSEY AREA PRESCRIBING COMMITTEE

PRESCRIBING POLICY STATEMENT

REF: PS80 FINAL

FIRST APC BOARD DATE: 29 JUN 2016

LAST APC BOARD DATE: 01 NOV 2017



Pan Mersey

Area Prescribing Committee

CANAGLIFLOZIN, DAPAGLIFLOZIN and EMPAGLIFLOZIN as MONOTHERAPIES : a multiple prescribing statement

GREEN

The Pan Mersey Area Prescribing Committee recommends the prescribing of CANAGLIFLOZIN, DAPAGLIFLOZIN and EMPAGLIFLOZIN as MONOTHERAPIES as options for treating type 2 diabetes in adults in accordance with NICE TA390.

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

NICE technology appraisal [TA390](#)¹ recommends canagliflozin, dapagliflozin and empagliflozin as MONOTHERAPIES as options 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

See NICE Guideline 28 Type 2 diabetes in adults: management² [algorithm](#) for where a DPP-4 inhibitor would otherwise be prescribed.

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](#)³
- 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](#)⁴

For the current advice on [SGLT-2 inhibitors as combination](#) therapy see the Pan Mersey APC prescribing policy statement

Please note: the effectiveness of SGLT-2 inhibitors is dependent on adequate renal function, see the Implementation Notes for the individual drugs for further details

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 MONOTHERAPY

<p>EFFECTIVENESS</p> <p>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.</p> <p>NICE TA 390 states that the SGLT-2 inhibitors have shown statistically significant improvements compared with placebo for the primary outcome of change in HbA1c. Reductions in weight compared with placebo had also been shown.¹</p> <p>NICE concluded that from the evidence available it was not possible to determine if there are any differences in effectiveness between the SGLT-2 inhibitors.¹</p>	<p>SAFETY^{3,4,5}</p> <p>Contraindications: hypersensitivity to the active ingredients or any of the excipients, type 1 diabetes, treatment of diabetic ketoacidosis.</p> <p>There is an increased rate of adverse reactions related to volume depletion (postural dizziness, orthostatic 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).</p> <p>Urinary tract infections, mostly mild to moderate, more frequently reported compared to placebo. No increase in incidence of recurrent infections.</p> <p>In subjects ≥ 75 years of age, a higher proportion had adverse reactions related to volume depletion.</p> <p>Limited experience in heart failure NYHA class III, none in NYHA class IV.</p> <p>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)</p> <p>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)</p> <p>Consult the SPC for full information.</p>												
<p>COST⁶ annual cost per patient</p> <table border="0"> <tr> <td>Canagliflozin:</td> <td>£477</td> </tr> <tr> <td>Dapagliflozin:</td> <td>£477</td> </tr> <tr> <td>Empagliflozin</td> <td>£477</td> </tr> <tr> <td>Sitagliptin</td> <td>£434</td> </tr> <tr> <td>Linagliptin</td> <td>£434</td> </tr> <tr> <td>Saxagliptin</td> <td>£412</td> </tr> </table> <p>NB: alogliptin is not licensed for monotherapy</p>	Canagliflozin:	£477	Dapagliflozin:	£477	Empagliflozin	£477	Sitagliptin	£434	Linagliptin	£434	Saxagliptin	£412	<p>PATIENT FACTORS⁵</p> <p>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/1.73m². Maximum dose of 100mg daily in patients with eGFR <60 ml/min/1.73m² No dosage adjustment for patients with eGFR ≥ 60 ml/min/1.73m²</p> <p>Hepatic impairment: Mild / moderate, no dosage adjustment. Severe, not recommended</p>
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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 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.

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 m².

DAPAGLIFLOZIN film coated tablets (Forxiga® ▼) as MONOTHERAPY

<p>EFFECTIVENESS</p> <p>Dapagliflozin 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.</p> <p>NICE TA390 states that the SGLT-2 inhibitors have shown statistically significant improvements compared with placebo for the primary outcome of change in HbA1c. Reductions in weight had compared with placebo had also been shown.¹</p> <p>NICE concluded that from the evidence available it was not possible to determine if there are any differences in effectiveness between the SGLT-2 inhibitors.¹</p>	<p>SAFETY^{3,4,7}</p> <p>Contraindications: hypersensitivity to the active substance or to any of the excipients, type 1 diabetes mellitus, treatment of diabetic ketoacidosis.</p> <p>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.</p> <p>Urinary tract infections more frequently reported compared to placebo, consider temporary interruption of dapagliflozin when treating pyelonephritis or urosepsis.</p> <p>In subjects ≥ 65 years of age, a higher proportion had adverse reactions related to renal impairment/failure and volume depletion.</p> <p>Limited experience in NYHA class I-II, none in NYHA class III-IV. 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)</p> <p>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)</p> <p>Consult the SPC for full information.</p>												
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PRESCRIBING INFORMATION

The recommended dose is 10 mg once daily at any time of day, with or without food. Tablets should be swallowed whole.

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 m².

EMPAGLIFLOZIN film coated tablets (Jardiance® ▼) as MONOTHERAPY

<p>EFFECTIVENESS</p> <p>Empagliflozin 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.</p> <p>NICE TA390 states that the SGLT-2 inhibitors have shown statistically significant improvements compared with placebo for the primary outcome of change in HbA1c. Reductions in weight had compared with placebo had also been shown. NICE concluded that from the evidence available it was not possible to determine if there are any differences in effectiveness between the SGLT-2 inhibitors.¹</p> <p>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.⁹</p>	<p>SAFETY^{3,4,8}</p> <p>Contraindications: hypersensitivity to the active ingredients or any of the excipients, type 1 diabetes, treatment of diabetic ketoacidosis.</p> <p>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.</p> <p>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 16)</p> <p>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)</p> <p>Consult the SPC for full information.</p>												
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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 \geq 60 ml/min/1.73 m². Care should be taken when increasing the dose for patients \geq 75 years, with cardiovascular disease or with other co-morbidities where the initial diuresis poses a risk.

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/1.73m² and should be discontinued if eGFR persistently < 45 ml/min/1.73 m². Max dose for eGFR 45-60 ml/min/1.73m² is 10mg.

REFERENCES

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