NHS
Pan Mersey
Area Prescribing Committee

CANAGLIFLOZIN, DAPAGLIFLOZIN, EMPAGLIFLOZIN and ERTUGLIFLOZIN as COMBINATION THERAPIES in type 2 diabetes: a multiple prescribing statement

The Pan Mersey Area Prescribing Committee recommends the prescribing of CANAGLIFLOZIN, DAPAGLIFLOZIN, EMPAGLIFLOZIN and ERTUGLIFLOZIN as COMBINATION THERAPIES as options for treating type 2 diabetes in adults in accordance with NICE guidance

GREEN

Canagliflozin, dapagliflozin, empagliflozin and ertugliflozin are selective sodium-glucose cotransporter-2 (SGLT-2) inhibitors. NICE technology appraisals TA315[1] TA288[2] TA418[3] TA336[4] TA572[5] and TA583[6] recommend SGLT-2 inhibitors as COMBINATION THERAPIES (dual and triple regimens) as options for treating type 2 diabetes in adults.

Canagliflozin, dapagliflozin, empagliflozin or ertugliflozin 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) [1][2][4][5]

Canagliflozin, dapagliflozin or empagliflozin in combination with insulin, with or without other antidiabetic drugs, [1][2][4] **or in a triple therapy regimen in combination with metformin and a sulfonylurea**[1][3][4]

Canagliflozin or empagliflozin in a triple therapy regimen in combination with metformin and pioglitazone[1][4]

Ertugliflozin in a triple therapy regimen with metformin and a dipeptidyl peptidase-4 (DPP-4) inhibitor when diet and exercise alone do not provide adequate glycaemic control, only if:

- the disease is uncontrolled with metformin and a DPP-4 inhibitor, and
- a sulfonylurea or pioglitazone is not appropriate.[6]

See NICE Guideline (NG) 28 Algorithm for blood glucose lowering therapy in adults with type 2 diabetes for where a DPP-4 inhibitor would otherwise be prescribed.[7]

See the separate Pan Mersey APC policy statement for the current advice on SGLT-2 inhibitors as monotherapy in type 2 diabetes. There are also statements for the use of dapagliflozin in type 1 diabetes and in heart failure.

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.

SGLT-2 inhibitors should be used with caution in patients with risk factors for diabetic ketoacidosis (DKA).

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.

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This recommendation has been designated suitable for inclusion on the Pan Mersey APC static list and will only be reviewed if significant new evidence becomes available.
APC administration provided by Midlands and Lancashire Commissioning Support Unit

Prescribing policy statement
Version: 2.0
STATIC

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

Effectiveness[1]

Canagliflozin 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 with metformin, canagliflozin provides broadly comparable glycaemic control to DPP-4 inhibitors 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 DPP-4 inhibitor 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 DPP-4 inhibitor and dapagliflozin.

Safety

Contraindications: hypersensitivity to the active ingredients or any of the excipients. Should not be used for treatment of type 1 diabetes. 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. Urinary tract infections, mostly mild to moderate, were more frequently reported compared to placebo. Pyelonephritis and urosepsis have been reported post-marketing. Vulvovaginal candidiasis (very common) and balanitis (common) have been reported in clinical studies.[8] Limited experience in heart failure New York Heart Association (NYHA) class III, none in NYHA class IV. Rare cases of diabetic ketoacidosis (DKA), including life-threatening cases, have been reported in patients treated with SGLT-2 inhibitors. SGLT-2 inhibitors should be used with caution in patients with risk factors for DKA.[9] In patients where DKA is suspected or diagnosed, canagliflozin should be discontinued immediately.[8] An increased risk of lower extremity amputations has been observed in trials in high cardiovascular (CV) risk patients.[10] Post-marketing reports of Fournier's gangrene have been associated with SGLT-2 inhibitors.[11] Enzyme inducers (such as St. John's wort, rifampicin, barbiturates, phenytoin, carbamazepine, ritonavir, efavirenz) may reduce effectiveness of canagliflozin. [8]
Consult the SPC for full information.

Cost[12]

Drug	Dosage	Annual cost per patient
Canagliflozin	100mg daily	£477
Dapagliflozin	10mg daily	£477
Empagliflozin	10mg daily	£477
Ertugliflozin	5mg daily	£383

Patient factors[8]

Efficacy is dependent on renal function and is reduced in moderate renal impairment and likely absent in severe renal impairment. Not recommended for initiation in patients with estimated glomerular filtration rate [eGFR] <30 ml/min/1.73m^2. Maximum dose of 100mg daily in patients with eGFR <60ml/min/1.73m^2.
Hepatic impairment: Mild / moderate, no dosage adjustment required. Severe, not recommended.

Prescribing information[8]

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 CV 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[8]

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

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

Effectiveness

Dapagliflozin lowers blood glucose by blocking the reabsorption of glucose in the kidneys and promoting excretion of excess glucose in the urine. As an add-on to metformin, dapagliflozin demonstrated a statistically significant reduction in HbA1c and body weight compared with placebo. As an add-on to insulin a statistically significant reduction in HbA1c and body weight and systolic blood pressure compared with placebo in one study of 12 weeks and one study of 24 weeks was seen.[2] 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.[3]

Safety

Contraindications: hypersensitivity to the active substance or to any of the excipients. 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. Elderly patients may be at a greater risk for volume depletion. Urinary tract infections (UTIs) were more frequently reported compared to placebo, consider temporary interruption of dapagliflozin when treating pyelonephritis or urosepsis. Vulvovaginitis, balanitis and related genital infections were more frequently reported compared to placebo. Experience with dapagliflozin in NYHA class IV is limited.[13] Rare cases of DKA, including life-threatening cases, have been reported in patients treated with SGLT-2 inhibitors. SGLT-2 inhibitors should be used with caution in patients with risk factors for DKA.[9] In patients where DKA is suspected or diagnosed, dapagliflozin should be discontinued immediately.[13] An increased risk of lower extremity amputations has been observed in trials in high CV risk patients.[10] Post-marketing reports of Fournier's gangrene have been associated with SGLT-2 inhibitors.[11] Consult the SPC for full information.

Cost[12]

Drug	Dosage	Annual cost per patient
Canagliflozin	100mg daily	£477
Dapagliflozin	10mg daily	£477
Empagliflozin	10mg daily	£477
Ertugliflozin	5mg daily	£383

Patient factors[13]

Efficacy is dependent on renal function and is reduced in moderate renal impairment and probably absent in severe renal impairment. Dapagliflozin should not be initiated in patients with a GFR < 60 mL/min and should be discontinued at GFR persistently below 45 mL/min. Dapagliflozin has not been studied in severe renal impairment (GFR < 30 mL/min) or end-stage renal disease (ESRD). No dosage adjustment for mild or moderate hepatic impairment. In patients with severe hepatic impairment, a starting dose of 5 mg is recommended.

Prescribing information[13]

The recommended dose is 10 mg once daily at any time of day, with or without food. Tablets should be swallowed whole. In severe hepatic impairment a starting dose of 5mg daily should be used, if tolerated and tighter glycaemic control is required the dose may be increased to 10 mg. 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.

Implementation notes[13]

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 with GFR < 60mL/min, monitoring is recommended at least 2 to 4 times per year. Discontinue dapagliflozin if GFR is persistently below 45 mL/min.

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

Effectiveness[4]
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 effective compared with placebo. Also, on the basis of the network meta-analyses, 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 DDP-4 inhibitors.

Safety
Contraindications: hypersensitivity to the active ingredients or any of the excipients. Should not be used for treatment of type 1 diabetes. In case of conditions that may lead to fluid loss, careful monitoring of volume status and electrolytes is recommended. Temporary interruption of treatment should be considered until fluid loss is corrected. In patients 75 years and older, an increased risk for volume depletion should be taken into account. Vaginal candidiasis and balanitis were reported more frequently compared to placebo. Experience in NYHA class I-II is limited, and there is no experience in clinical studies with empagliflozin in NYHA class III-IV. [14] Rare cases of DKA, including life-threatening cases, have been reported in patients treated with SGLT-2 inhibitors. SGLT-2 inhibitors should be used with caution in patients with risk factors for DKA.[9] In patients where DKA is suspected or diagnosed, empagliflozin should be discontinued immediately. [14] An increased risk of lower extremity amputations has been observed in trials in high CV risk patients.[10] Post-marketing reports of Fournier's gangrene have been associated with SGLT-2 inhibitors.[11] Concomitant treatment with inducers of UGT enzymes (e.g. rifampicin or phenytoin) is not recommended due to the potential risk of decreased efficacy of empagliflozin[14]. Consult the SPC for full information.

Cost[12]

Drug	Dosage	Annual cost per patient
Canagliflozin	100mg daily	£477
Dapagliflozin	10mg daily	£477
Empagliflozin	10mg daily	£477
Ertugliflozin	5mg daily	£383

Patient factors[14]
No dose adjustment required for patients with eGFR ≥60 ml/min/1.73m^2. Should not be initiated in patients with eGFR <60 ml/min/1.73 m^2 and should be discontinued if eGFR persistently < 45 ml/min/1.73 m^2. Maximum dose for eGFR 45-60 ml/min/1.73m^2 is 10mg. Should not be used in patients with ESRD or in patients on dialysis. Initiation in patients aged 85 years and older is not recommended. Hepatic impairment: Mild/moderate, no dosage adjustment. Severe, not recommended.

Prescribing information[14]

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 m^2. Care should be taken when increasing the dose for patients > 75 years, with CV disease or with other co-morbidities where the initial diuresis poses a risk. In patients tolerating empagliflozin whose eGFR is persistently below 60 ml/min/1.73m^2, dose should be maximum 10 mg once daily. 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[14]

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.

ERTUGLIFLOZIN film-coated tablets (Steglatro® ▼) as COMBINATION THERAPY

Effectiveness

Ertugliflozin lowers blood glucose by blocking the reabsorption of glucose in the kidneys and promoting excretion of excess glucose in the urine. NICE TA583 concluded that ertugliflozin appears to have similar health benefits to other SGLT-2 inhibitors when taken with metformin and a DPP-4 inhibitor, and has a lower acquisition cost than other SGLT-2 inhibitors. It has only been compared with other SGLT-2 inhibitors, not with other third-line treatments for type 2 diabetes (sulfonylureas or pioglitazone), and is therefore recommended only if a sulfonylurea or pioglitazone is not appropriate.[5] NICE TA572 concluded that indirect comparisons demonstrate that ertugliflozin has similar overall health benefits to canagliflozin, dapagliflozin and empagliflozin and the acquisition cost of ertugliflozin is lower. It is therefore recommended as an option for treating type 2 diabetes as monotherapy or with metformin.[6]

Safety

Contraindications: hypersensitivity to the active ingredient or any of the excipients. Should not be used for treatment of type 1 diabetes. Ertugliflozin causes osmotic diuresis, which may cause symptomatic hypotension, particularly in impaired renal function, elderly, patients on diuretics or on anti-hypertensives with a history of hypotension. Before initiation, volume status should be assessed and corrected if indicated. In case of conditions that may lead to fluid loss (e.g. GI illness), careful monitoring of volume status and electrolytes is recommended and temporary interruption of ertugliflozin considered until the fluid loss is corrected. Urinary glucose excretion may be associated with an increased risk of urinary tract infections. Temporary interruption of ertugliflozin should be considered when treating pyelonephritis or urosepsis. Increased risk of genital mycotic infections. Limited experience in heart failure NYHA class I - II, none in NYHA class III – IV.[15] Rare cases of DKA, including life-threatening cases, have been reported in patients treated with SGLT-2 inhibitors. SGLT-2 inhibitors should be used with caution in patients with risk factors for DKA[9] In patients where DKA is suspected or diagnosed, ertugliflozin should be discontinued immediately.[15] An increased risk of lower extremity amputations has been observed in trials in high CV risk patients.[10] Post-marketing reports of Fournier's gangrene have been associated with SGLT-2 inhibitors.[11] Consult the SPC for full information.

Cost[12]

Drug	Dosage	Annual cost per patient
Canagliflozin	100mg daily	£477
Dapagliflozin	10mg daily	£477
Empagliflozin	10mg daily	£477
Ertugliflozin	5mg daily	£383

Patient factors[15]

Should not be initiated in patients with an eGFR <60 ml/min/1.73 m^2. Discontinue when eGFR is persistently <45 ml/min/1.73 m^2. Should not be used in patients with severe renal impairment, with ESRD, or receiving dialysis. Limited experience in patients ≥ 75 years of age. Hepatic impairment: Mild/moderate, no dosage adjustment. Severe, not recommended.

Prescribing information[15]

The recommended starting dose is 5 mg once daily. In patients tolerating ertugliflozin 5 mg once daily, the dose can be increased to 15 mg once daily if additional glycaemic control is needed. Ertugliflozin should be taken orally once daily in the morning, with or without food. In case of swallowing difficulties, the tablet could be broken or crushed. When ertugliflozin is used in combination with an insulin secretagogue, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycaemia.

Implementation notes[15]

Renal function should be monitored prior to initiation of ertugliflozin and periodically thereafter. Monitoring is required more frequently in patients with an eGFR below 60 ml/min/1.73 m^2. Additional monitoring is recommended prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter. Ertugliflozin should not be initiated in patients with an eGFR <60 ml/min/1.73m2 and should be discontinued if eGFR is persistently below 45 ml/min/1.73m^2.

CANAGLIFLOZIN, DAPAGLIFLOZIN, EMPAGLIFLOZIN and ERTUGLIFLOZIN as COMBINATION THERAPIES in type 2 diabetes: a multiple prescribing statement

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

- MHRA Drug Safety Update; SGLT2 inhibitors: updated advice on the risk of diabetic ketoacidosis (April 2016).[9]
- MHRA Drug Safety Update; SGLT2 inhibitors: updated advice on increased risk of lower-limb amputation (mainly toes) (March 2017). [10]
- MHRA Drug Safety Update; SGLT2 inhibitors: reports of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum) (February 2019).[11]
- MHRA Drug Safety Update; SGLT2 inhibitors: monitor ketones in blood during treatment interruption for surgical procedures or acute serious medical illness (March 2020).[16]

References

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