Dapagliflozin (Forxiga) and canagliflozin (Invokana)

KEY POINTS

A new class of oral treatment for type 2 diabetes
Sodium–glucose co-transporter-2 (SGLT2) inhibitors block glucose reabsorption in the kidneys, so efficacy is dependent on kidney function.

SGLT2 inhibitors are PBS listed for dual combination therapy
Use in dual therapy in combination with metformin or a sulfonylurea in patients who are not able to be adequately controlled with metformin and a sulfonylurea.

Comparable efficacy and safety, in dual combination with metformin or a sulfonylurea, to that of metformin combined with a sulfonylurea
SGLT2 inhibitors provide another add-on option to improve glycaemic control in combination with metformin or a sulfonylurea, with a low risk of hypoglycaemic events except when combined with a sulfonylurea.

SGLT2 inhibitors are associated with modest weight loss
Caloric loss in urine is associated with modest weight loss and reduced abdominal obesity.

Increase in glycosuria leads to a higher risk of urogenital infections
Taking SGLT2 inhibitors is associated with an increased risk of mild to moderate urogenital tract infections.

Effects on diabetes-related complications and mortality are unknown
There are no long-term data on the effects of SGLT2 inhibitors on macrovascular disease, diabetes-related complications and mortality.

PBS listing

Authority required
Dapagliflozin (Forxiga) and canagliflozin (Invokana) are listed on the PBS as dual oral therapy in combination with either metformin or a sulfonylurea in people with type 2 diabetes mellitus who are not able to be adequately controlled by treatment with a combination of metformin and a sulfonylurea.

Patients must have, or have had, an HbA1c > 7%* before starting a dipeptidyl peptidase 4 (DPP-4) inhibitor (‘gliptin’), a thiazolidinedione (‘glitazone’), a glucagon-like peptide-1 (GLP-1) analogue or an SGLT2 inhibitor.

The date and level of the HbA1c measurement† must be, or must have been, documented in the patient’s medical record at the time treatment with a gliptin, glitazone, GLP-1 analogue or SGLT2 inhibitor was started, and the measurement must be, or have been, performed no more than 4 months before treatment was started.

SGLT2 inhibitors are not PBS subsidised for use in combination with both metformin and a sulfonylurea (triple oral therapy), as monotherapy or in combination with an insulin, a glitazone, a gliptin or a GLP-1 analogue, although these uses are TGA approved.‡

May be prescribed by nurse practitioners
SGLT2 inhibitors may be prescribed by nurse practitioners as continuing therapy only, when the treatment and prescribing of medicine for a patient has been initiated by a medical practitioner.

See the PBS website for more information on nurse practitioner PBS prescribing.

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Additional information

www.pbs.gov.au/browse/nurse

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* Reporting for HbA1c has changed from a percentage to the unit mmol/mol in most international guidelines; however, to align with earlier PBS listings, HbA1c will continue to be referred to as a percentage in this article. The conversion for 7% is 53 mmol/mol.

† When clinically inappropriate, blood glucose monitoring will be accepted as an alternative to HbA1c. Refer to www.pbs.gov.au for detailed clinical criteria.

‡ Refer to the Product Information provided by the manufacturers for details.

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PBS: pharmaceutical benefits scheme  HbA1c: glycosylated haemoglobin A1c
What are they?

Dapagliflozin and canagliflozin are the first PBS-listed agents from a new class of oral antidiabetics known as SGLT2 inhibitors. This class represents a novel insulin-independent approach for treatment of type 2 diabetes that relies on the role of the kidneys in glucose homeostasis.

SGLT2 is a low-affinity, high-capacity sodium-coupled glucose transporter located on the luminal side of the renal proximal tubule and accounts for most glucose reabsorption in the kidneys. In non-diabetic people around 180 g per day of glucose is freely filtered by the kidneys but nearly all is reabsorbed by SGLT2, with loss in urine occurring only when plasma glucose exceeds a threshold for reabsorption.

In type 2 diabetes, even when hyperglycaemia occurs, filtered glucose continues to be reabsorbed, leading to persistently elevated blood glucose concentrations. By selectively and reversibly inhibiting SGLT2, dapagliflozin and canagliflozin lower plasma glucose levels through decreased reabsorption of glucose and increased urinary glucose excretion, creating a diuretic effect.

Who are they for?

Both dapagliflozin and canagliflozin are TGA approved as an adjunct to diet and exercise for glycaemic control in adults with type 2 diabetes mellitus as:

- monotherapy when metformin is contraindicated or not tolerated
- add-on dual combination therapy, with metformin, a sulfonylurea or insulin (dapagliflozin and canagliflozin) or with other anti-hyperglycaemic agents (canagliflozin only).

Only dual combination therapy with metformin or a sulfonylurea is PBS subsidised (see ‘PBS listing’, page 3).

Do not use in type 1 diabetes

SGLT2 inhibitors, including dapagliflozin and canagliflozin, have not been studied in type 1 diabetes.

Contraindicated in impaired kidney function

Treatment benefit with SGLT2 inhibitors is dependent on kidney function, so efficacy may be affected in people with kidney impairment.

Dapagliflozin is contraindicated in people with moderate or severely impaired kidney function (eGFR < 60 mL/min/1.73 m² or CrCl < 60 mL/min).

Canagliflozin is contraindicated in people with severely impaired kidney function, including patients receiving dialysis (eGFR < 30 mL/min/1.73 m² or CrCl < 30 mL/min), or with eGFR persistently < 45 mL/min/1.73 m² or CrCl persistently < 45 mL/min.

Be vigilant in people with intravascular volume depletion

SGLT2 inhibitors contribute to osmotic diuresis and elevated urinary volume, with an accompanying reduction in sodium reabsorption in the kidneys.

Consider the diuretic effect of SGLT2 inhibitors before starting dapagliflozin or canagliflozin, especially in people who have reduced intravascular volume or those at risk of volume depletion. This includes people already taking diuretics or medicines with a diuretic effect and those with a history of hypotension (see ‘Dosing and monitoring issues’, page 9).

Limited data in people with severe hepatic impairment

Do not use dapagliflozin or canagliflozin in people with severe hepatic impairment, as there are limited clinical data or experience in this population.

Use in older people

Before starting dapagliflozin or canagliflozin in older people consider that they are more likely to have impaired kidney function and risk of volume depletion, which may be exacerbated by other concurrent medicines.

A starting dose of canagliflozin 100 mg once daily is recommended in patients aged 75 years or older. As a result of limited therapeutic experience, starting dapagliflozin in patients 75 or older is not recommended.

Avoid use in pregnancy and lactation

There are no data to support using SGLT2 inhibitors in pregnant women. Canagliflozin is listed as a pregnancy category C drug, while dapagliflozin has been designated category D by the manufacturers.
EVIDENCE SNAPSHOT

WHAT IS KNOWN ABOUT THESE DRUGS?

In comparison with other combination therapies, both dapagliflozin and canagliflozin provide similar improvements in HbA1c levels when combined with metformin or a sulfonylurea.

SGLT2 inhibitors contribute to weight loss mainly through a reduction in visceral adiposity and are associated with reduced systolic blood pressure mostly related to osmotic diuresis.

The mechanism of action and therefore efficacy depends on adequate kidney function.

The incidence of hypoglycaemia is not increased when an SGLT2 inhibitor is combined with metformin but there is a greater risk when combined with a sulfonylurea.

Due to increased glycosuria there is a risk of urogenital infections (e.g. UTI, vulvovaginal candidiasis, balanitis).

AREAS OF UNCERTAINTY

The long-term safety profile of SGLT2 inhibitors is not yet known and there are insufficient data to determine effects on macrovascular disease or diabetes-related complications and mortality.

It is unclear how elevated glycosuria associated with the mechanism of action for SGLT2 inhibitors impacts the urogenital tract, particularly with respect to urogenital infections.

An increased frequency of breast, bladder and prostate tumours was identified during the clinical program in people taking dapagliflozin, and will be further investigated in postmarketing surveillance.

WHAT DOES NPS SAY?

SGLT2 inhibitors are an alternative add-on treatment to improve glycaemic control in type 2 diabetes in dual therapy in combination with metformin (preferred combination) or a sulfonylurea, when the condition is not able to be adequately controlled by a combination of metformin and a sulfonylurea.

SGLT2 inhibitors may have reduced efficacy when kidney function is impaired and may not be appropriate in patients at risk of intravascular volume depletion.

Where do they fit?

Use metformin first line

While there is uniform agreement across guidelines about the role and benefits of metformin as a first-line drug treatment, there is some debate about recommendations for subsequent drugs to intensify treatment.

The latest guidelines in Australia recommend a target HbA1c ≤ 53 mmol/mol (7%) and, when metformin monotherapy (along with diet and exercise) inadequately controls blood glucose at this level, adding a sulfonylurea.
SGLT2 inhibitors in dual add-on therapy for glycaemic control

When a combination of metformin and sulfonylurea inadequately controls blood glucose, SGLT2 inhibitors (either dapagliflozin or canagliflozin) are a treatment option for use in dual add-on therapy with either metformin or a sulfonylurea.

Other PBS-listed alternatives to SGLT2 inhibitors include:
- insulin (usually basal)
- DPP-4 inhibitors
- glitazones
- a GLP-1 analogue
- an alpha-glucosidase inhibitor

Although they have TGA-approved indications, dapagliflozin and canagliflozin are not PBS subsidised as monotherapy or in dual therapy with insulin, a DPP-4 inhibitor, a glitazone, or a GLP-1 analogue, or in triple combination therapy with any other diabetes drugs.

Long-term safety and efficacy effects are unknown

Base choice of anti-diabetic drug on patient factors that include:
- individual HbA₁c level
- risk of inducing hypoglycaemia or weight gain
- impact of kidney or liver disease
- associated cardiovascular complications of hypertension and dyslipidaemia.

UK guidelines recommend considering dapagliflozin in dual therapy in line with recommendations for DPP-4 inhibitors, i.e. as second-line therapy to metformin instead of sulfonylurea (provided the sulfonylurea is contraindicated or not well tolerated) if a person is at significant risk of hypoglycaemia or its consequences.

SGLT2 inhibitors may suit people whose hyperglycaemia cannot be controlled with a combination of metformin and a sulfonylurea and who have a high risk of hypoglycaemia. However, in choosing add-on therapy, consider that the long-term effects of this drug class are not yet known.

SGLT2 inhibitors have not been shown to reduce the risk of macrovascular disease or diabetes-related complications and mortality and carry safety concerns that make them an unsuitable choice for certain people (see ‘Who are they for?’, page 4, and ‘Safety issues’, page 7).

How do they compare?

As a new class of drug there are limited postmarketing studies and relatively few published clinical trials on the efficacy and safety of SGLT2 inhibitors for managing type 2 diabetes.

The evidence to date shows that adding dapagliflozin or canagliflozin to either metformin or a sulfonylurea improves glycaemic control in people inadequately controlled with metformin or a sulfonylurea, although the effects on cardiovascular risk are undetermined at this time.

Add-on therapy with metformin or sulfonylurea improves glycaemic control

SGLT2 inhibitors provide effective and sustained glycaemic control for people inadequately controlled on metformin or a sulfonylurea.

In trials the placebo-adjusted reduction in mean HbA₁c achieved by adding either dapagliflozin 10 mg once daily or canagliflozin 100 mg or 300 mg once daily to metformin ranged from 0.54% to 0.77%, with a comparable reduction seen when dapagliflozin was added to a sulfonylurea.

There are no peer-reviewed data comparing canagliflozin with placebo in combination with a sulfonylurea, although data presented in the manufacturer’s Product Information suggest comparable efficacy to that achieved by a combination of canagliflozin added to metformin.

Comparable efficacy to that of alternative dual therapy combinations

A combination of either dapagliflozin 10 mg once daily or canagliflozin 100 mg once daily with metformin provides comparable improvement in glycaemic control to that achieved by a combination of metformin with a sulfonylurea.

The combination of canagliflozin 100 mg once daily with metformin provides comparable improvement to that achieved by sitagliptin with metformin.
Canagliflozin 300 mg once daily in combination with metformin reduced HbA1c by 0.10% and 0.15% more than a combination of metformin and a sulfonylurea,17 and a combination of metformin with sitagliptin,16 respectively.

There are no head-to-head studies comparing the relative efficacy of these two SGLT2 inhibitors.

**SGLT2 inhibitor effects on weight loss**
Most of the available weight-loss data relate to dapagliflozin 10 mg once daily; trials have shown a significant placebo-adjusted mean reduction in total body weight of 1.54–2.24 kg at 24 weeks’ treatment,14,15,18,20,21 which was sustained over nearly 2 years of treatment.20,21

There are fewer peer-reviewed data for the weight-loss effects associated with canagliflozin but the available data suggest placebo-adjusted weight loss ranging from 2.2 to 2.5 kg at 26 weeks that is sustained at 1 year.16

In dual combination with metformin, when either dapagliflozin 10 mg once daily or canagliflozin 100 mg or 300 mg once daily were added, weight loss was about 2–5 kg greater than when combined with a sulfonylurea,17,19 and for canagliflozin compared with sitagliptin.16

Overall, add-on therapy with SGLT2 inhibitors is associated with changes in body composition and weight loss comparable to those seen in non-pharmacological interventions including lifestyle modification and diet intervention.22

The clinical significance of these effects in Australian treatment populations needs to be evaluated in light of the fact that most of the study populations were overweight (e.g. BMI > 27 kg/m²).14-19

**Dapagliflozin is associated with a reduction in abdominal obesity**
Trials have shown a mean decrease in waist circumference of 1.20–1.52 cm at 24 weeks compared with placebo,14,15 with a small but statistically significant reduction in visceral adipose tissue leading to overall mean loss in fat mass of 1.48 kg measured by dual-energy X-ray absorptiometry.15

These effects were maintained at 102 weeks of treatment, with mean reduction in waist circumference of 2.1 cm and mean loss of fat mass of 1.34 kg compared with placebo.21 The clinical relevance of these effects is unclear.

**SGLT2 inhibitor effects on blood pressure**
At 24–26 weeks’ treatment in clinical trials, small reductions in systolic blood pressure of 4–6 mmHg (placebo adjusted) were observed for dapagliflozin added to metformin14 or a sulfonylurea18 and canagliflozin added to metformin.16

These studies also showed an accompanying rise in haematocrit or haemoglobin, which suggests that osmotic diuresis may have contributed to the drop in blood pressure.14,16,18 The clinical and long-term significance of these effects is unclear.

**The effect of SGLT2 inhibitors on morbidity and mortality is unknown**
Unlike metformin, which reduces the incidence of diabetes-related complications and mortality,23 or sulfonylureas and insulin, both of which reduce the incidence of microvascular complications,24 there are no long-term data on the effects of SGLT2 inhibitors on diabetes-related complications and mortality. Trials designed to confirm the long-term impact of SGLT2 inhibitors on cardiovascular outcomes are in progress.25,26

**Safety issues**
The long-term safety profile of SGLT2 inhibitors is not yet known. In clinical trials of add-on therapy with dapagliflozin or canagliflozin, adverse events rarely led to discontinuation and typically related to:3,4

- genital and urinary tract infections14,16-18,20
- respiratory and gastrointestinal disorders14,16-18,20
- non-specific symptoms such as headache, back pain or rash14,16-18,20
- osmotic diuresis-related or volume-depletion-related effects.
Given the mechanism of action of SGLT2 inhibitors, adverse effects such as genital infection and UTIs, volume depletion (hypovolaemia-related events and haemoconcentration) and kidney safety and hypoglycaemia have been a focus of safety and tolerability in clinical trials to date.

For information about reporting adverse reactions to the TGA, or to report suspected adverse reactions online, see the TGA website (www.tga.gov.au/safety/problem.htm#medicine) or use the ‘Blue Card’ distributed with the October issue of Australian Prescriber.

**Urogenital tract infections are common**

In clinical trials, add-on treatment with SGLT2 inhibitors has consistently been associated with a higher incidence of genital infections, with vulvovaginal candidiasis in women and balanitis in men most frequently reported. 3,4,14,16–20,27–29

The elevated risk was confirmed in a recent meta-analysis of six add-on therapy trials showing more than a threefold higher risk of genital infections, with a mean rate of 9.5% and 2.6% for 10 mg dapagliflozin and placebo, respectively. 30

There are fewer published data for canagliflozin but the evidence to date suggests that this is a class effect for SGLT2 inhibitors related to the mechanism of action.

Overall, UTIs during treatment with SGLT2 inhibitors are less frequent than genital infections. A pooled analysis showed only a slight increase in the risk of bacteriuria on repeated urinalysis (suggestive of UTI), with a mean incidence of 8.8% and 6.1% for dapagliflozin and placebo, respectively. 30

In contrast to the consistently increased incidence of genital infections, the evidence for UTIs is more variable. In some placebo-controlled studies there were no significant differences in the incidence of UTIs in people taking dapagliflozin in combination with metformin14 or sulfonylurea.18

Similarly, in people taking canagliflozin 100 mg or 300 mg once daily the incidence of UTI was only slightly higher than that for placebo and glimepiride17 and, with the higher dose (300 mg), less than the rate of UTIs for sitagliptin 100 mg once daily.16

**Urogenital infections more common in women and people with prior history**

Women taking SGLT2 inhibitors tend to have a higher incidence of infection than men, 3,4,16–20,27,28 and the risk may be higher in people with a history of recurrent genital infection or UTI.4

Most infections appear in the first 24–26 weeks of treatment6,20,28 and, while recurrent infections are possible, most involve a single occurrence.3,14,27,28

Infections are typically of mild or moderate severity and resolve with conventional treatment and in trials did not lead to patient discontinuation.3,4,14,16–20,27,28

A large UK study authored by the sponsors of dapagliflozin found that patients with diabetes, particularly those with poorly controlled diabetes, are at an elevated risk of being diagnosed with genital infections compared with those without diabetes.31

Because the mechanism of action of SGLT2 inhibitors is known to induce glycosuria, the increased risk of urogenital infections is an expected and manageable side effect. Nevertheless, the long-term effects of elevated glycosuria on the urogenital tract associated with SGLT2 inhibitor treatment remain unknown.

**Low risk of hypoglycaemia unless combined with a sulfonylurea**

Owing to a mechanism of action that is independent of insulin, hypoglycaemia is not an expected adverse effect of SGLT2 inhibitors.

Trials have shown no significant increase in the rate of hypoglycaemia when dapagliflozin is added to metformin in dual combination.4,14,20 However, more people reported hypoglycaemia when dapagliflozin was added to a sulfonylurea (7.9%) than with placebo (4.8%).18

The incidence of hypoglycaemia was lower when dapagliflozin or canagliflozin were used in combination with metformin compared with metformin in combination with a sulfonylurea,17,19 and similar for canagliflozin compared with sitagliptin.18

If starting an SGLT2 inhibitor with a sulfonylurea, a lower dose of sulfonylurea may be required to reduce the risk of hypoglycaemia.
Concerns related to cancer
In 2011 an FDA advisory committee voted against approving dapagliflozin, citing concerns over the emergence of an apparent risk for breast and bladder cancer in the treatment arms of their analysis.32
In their assessment the European Medicines Agency (EMA) found a small but higher number of breast, bladder and prostate cancer cases when they considered dapagliflozin, although their analysis showed no difference in the overall cancer risk between dapagliflozin compared with placebo.33
A causal relationship with dapagliflozin is considered unlikely, given the short latency period between first drug exposure and tumour diagnosis; however, the manufacturer is investigating the risk in postmarketing surveillance.4
The FDA found the overall incidence of renal, bladder and breast cancers was low in the clinical program for canagliflozin, and there was no increase in the incidence of these cancers in the canagliflozin treatment groups compared with those not receiving canagliflozin.34

Dosing in impaired kidney function
It is not necessary to adjust the dose of dapagliflozin in people with mild kidney impairment, but do not use dapagliflozin in patients with moderate or severe kidney impairment (eGFR < 60 mL/min/1.73 m² or CrCl < 60 mL/min).
No dose adjustment is required based on age alone, but consider kidney function and the risk of volume depletion before prescribing in older people, noting that dapagliflozin is not recommended in people over 75. Discontinue treatment with dapagliflozin if kidney function falls below eGFR < 60 mL/min/1.73 m² or CrCl < 60 mL/min.4
Consider a lower dose of canagliflozin (100 mg once-daily) in patients over 75 and those with eGFR < 60 mL/min/1.73 m² or CrCl < 60 mL/min.
Only increase the dose to 300 mg once daily if the 100 mg dose is well tolerated and tighter glycaemic control is needed. Discontinue treatment when eGFR is persistently < 45 mL/min/1.73 m² or CrCl is < 45 mL/min.5

Check kidney function in people with impaired kidney function
Effective treatment with SGLT2 inhibitor is dependent on kidney function, so it is recommended to assess kidney function:
- before starting an SGLT2 inhibitor and at least annually thereafter
- when starting other medicines known to reduce kidney function, and periodically thereafter
- in patients whose kidney function approaches moderate kidney impairment, at least 2–4 times a year.3,4

Dosing in hepatic impairment
Dose adjustments are not needed for mild or moderate hepatic impairment, but do not use dapagliflozin or canagliflozin in patients with severe hepatic impairment.3,4

Reason for PBS listing
The PBAC recommended the listing of dapagliflozin and canagliflozin on the PBS on a cost-minimisation basis with sitagliptin. The equi-effective doses are dapagliflozin 10 mg, canagliflozin 300 mg and sitagliptin 100 mg.

Dosing and monitoring issues
The recommended dose of dapagliflozin as an add-on in dual combination therapy with metformin or a sulfonylurea is 10 mg taken once daily at any time of the day regardless of meals.4
The recommended dose of canagliflozin as an add-on in dual combination therapy with metformin or a sulfonylurea is 100 mg or 300 mg once daily. The higher dose is for use in patients with eGFR ≥ 60 mL/min/1.73 m² or CrCl ≥ 60 mL/min and those who have a low risk of adverse reactions associated with intravascular volume depletion.3
Interrupt dapagliflozin if treating pyelonephritis or urosepsis
In trials, pyelonephritis was an uncommon adverse event and presented in similar frequencies in people treated with dapagliflozin and placebo. The increased risk of urogenital infection associated with glycosuria may require temporary interruptions in treatment with dapagliflozin when treating pyelonephritis or urosepsis. Discontinuation of dapagliflozin may be considered if people develop recurrent UTIs.\(^4\)

Assess and monitor the risk of volume depletion
Before starting an SGLT2 inhibitor, assess and correct intravascular volume in people who may be volume depleted, and monitor for signs and symptoms or conditions (e.g. vomiting, diarrhoea, heat stress or severe infections) that may lead to volume depletion.\(^1,4\)

A starting dose of canagliflozin 100 mg is recommended in people taking a loop diuretic.\(^3\)

Information for patients
Advise people taking SGLT2 inhibitors, or carers administering these, as follows.

- Tell your healthcare professional if symptoms that indicate reduced body fluids occur while taking SGLT2 inhibitors (e.g. dry mouth, severe thirst, severe diarrhoea or vomiting, dizziness, or urinating less often than normal or not at all) or if a condition that will lead to dehydration develops (e.g. vomiting, diarrhoea or a severe infection).
- SGLT2 inhibitors work like a diuretic by increasing glucose excretion in urine and may lead to a loss of needed body fluids or dehydration. People taking a loop diuretic should tell their doctor.
- Seek urgent medical attention if rash, hives, shortness of breath, wheezing, difficulty breathing, swelling of the face, lips or tongue occur or if you feel faint during treatment.
- Genital yeast infections are a common side effect, and treatment also increases the chance of getting a urinary tract infection, especially in people with a prior history. Seek medical advice if you experience painful urination, frequent or urgent need to urinate or blood in the urine, soreness or more severe irritation and swelling of your genitals.
- If you are pregnant or become pregnant dapagliflozin or canagliflozin may be harmful to the unborn baby and should not be taken. For women of childbearing age, speak with your doctor about contraception and tell your doctor if you are, or intend to become, pregnant or if you are, or will start, breastfeeding. Speak with your health professional about other treatments for diabetes if you are breastfeeding.

Ensure patients understand that they should consult a health professional before taking non-prescription medicines that can adversely affect kidney function, such as non-steroidal anti-inflammatory drugs.

As treatment effects of dapagliflozin and canagliflozin are dependent on kidney function, additional tests to monitor kidney function may be needed in people with worsening kidney function.

People with poor kidney function should not use dapagliflozin or canagliflozin, as these drugs are rendered less effective.

Dapagliflozin and canagliflozin improve glycaemic control with a low risk of hypoglycaemia but the long-term benefits and adverse effects of these drugs are not yet fully known.

As with all treatments for type 2 diabetes, encourage patients to adopt or maintain a healthy diet and exercise regularly, as these are important for controlling blood sugar in conjunction with prescribed medicines. Advise patients that treatment is long term.

Low blood sugar levels may occur, especially when treatment includes a sulfonylurea or insulin, and care should be taken when driving or operating machinery until the effects of new treatment for the person are known.

REFERENCES

Dapagliflozin (Forxiga) and canagliflozin (Invokana)
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