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New Drug Update

Canagliflozin: a novel 'glucuretic' approach for the treatment of type 2 diabetes mellitus

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ABSTRACT

Canagliflozin is the first in a new class of glucose-lowering drugs, an oral inhibitor of sodium glucose cotransporter 2 (SGLT2). SGLT2, the transporter is responsible for reabsorbing the majority of glucose filtered by the kidney. SGLT2 inhibitors are a new class of oral drugs indicated only for the treatment of type 2 diabetes mellitus in conjunction with exercise and a healthy diet. They inhibit glucose re-absorption in the proximal renal tubules providing an insulin independent mechanism to lower blood glucose. Their use in clinical studies is associated with improved glycemic control, weight loss, and a low risk of hypoglycemia. They have been studied alone and with other medications including sulfonylureas, sitagliptin, and insulin.

Keywords: Sodium-glucose cotransporter 2, Canagliflozin, Diabetes mellitus type 2

INTRODUCTION

Canagliflozin (*Invokana*, Janssen Pharmaceuticals) is the first in a new class of glucose-lowering drugs, an oral inhibitor of sodium glucose cotransporter 2 (SGLT2). SGLT2 is a low-affinity; high capacity glucose transporter located in the S1 segment of proximal tubule in the kidneys and is responsible for 90% of glucose reabsorbing the majority of glucose filtered by the kidney.[1] Canagliflozin provides SGLT2 inhibition, reducing reabsorption of glucose in the kidney, resulting in increased urinary glucose excretion, with a consequent lowering of plasma glucose levels as well as weight loss.[2] While canagliflozin is the first SGLT2 inhibitor to reach the market in the United States, another drug in this class, dapagliflozin (*Forxiga*, Bristol-Myers Squibb/AstraZeneca), is already approved and available in Europe since November, 2012. The US FDA denied approval of dapagliflozin in January, 2012 because of concerns about a cancer signal. Canagliflozin, which has also been submitted for approval in the European Union, does not appear to share that risk, with no signal for an increase in malignancy in about 8000 person-years of exposure. The US FDA approved canagliflozin (*Invokana*, Janssen Pharmaceuticals) on March 29, 2013, with the requirement that the company perform five separate post marketing studies: a cardiovascular outcomes trial; an enhanced pharmacovigilance program to monitor for malignancies, serious cases of pancreatitis, severe hypersensitivity reactions, photosensitivity reactions, liver abnormalities, and adverse pregnancy outcomes; a bone safety study; and two pediatric studies under the Pediatric Research Equity Act, including a pharmacokinetic and pharmacodynamic study and a safety and efficacy study. Among these is the completion of the ongoing cardiovascular outcomes trial,

Canagliflozin Cardiovascular Assessment Study (CANVAS), which the company is conducting to fulfill the 2008 FDA guidance regarding cardiovascular safety for investigational diabetes drugs. Final results of CANVAS, which enrolled a total of 4,330 individuals with cardiovascular disease (CVD) or at high risk for it, are not expected until 2015.

DRUG DESCRIPTION

Canagliflozin (INVOKANA, *Janssen Pharmaceuticals*) is supplied as film-coated tablets for oral administration, containing 100 mg and 300 mg of canagliflozin (anhydrous form).

Indications

Canagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[3] It is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Dosage

The recommended starting dose of canagliflozin is 100 mg once daily, taken before the first meal of the day. In those patients that require additional glycemic control, the dose can be increased to 300 mg once daily provided they have good renal function. No dose adjustment is needed in patients with mild renal impairment (GFR of 60 mL/min/1.73 m²).

PHARMACODYNAMICS: MECHANISM OF ACTION

Sodium-dependent glucose cotransporters (or sodium-glucose linked transporter, SGLT) are a family of glucose transporter found in the enterocytes of the small intestine (SGLT1) and the proximal convoluted tubule of the nephron (SGLT2). SGLT2, expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. By inhibiting SGLT2, canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose (RTG), and thereby increases urinary glucose excretion.[4]

PHARMACOKINETICS

Absorption

Bioavailability: 65% and Peak plasma time: 1-2 hr.

Distribution

Protein bound: 99% (predominantly to albumin) and volume of distribution (Vd): 119 L.

Metabolism

O-glucuronidation is the major metabolic elimination pathway, mainly by UGT1A9 and UGT2B4 to 2 inactive O-glucuronide metabolites and CYP3A4-mediated (oxidative) metabolism is minimal (~7%).

Elimination

Half-life: 10.6 hr (100 mg dose); 13.1 hr (300 mg dose).

Total body clearance: 192 mL/min.

Excretion

Feces: 41.5% (canagliflozin), 7% (hydroxylated metabolite), 3.2% (O-glucuronide metabolite).

Urine: 33% excreted in urine, mainly as O-glucuronide metabolites (30.5%); <1% excreted unchanged.

Clinical results

In clinical trials, canagliflozin improved hemoglobin A1c (HbA1c) levels and fasting and postprandial blood glucose levels and was associated with weight loss in patients with type 2 diabetes. The safety and efficacy of the drug were tested in nine clinical trials involving more than 10,000 patients with type 2 diabetes. Canagliflozin monotherapy helped more patients achieve the American Diabetes Association (ADA)-recommended HbA1c goal of <7.0% over 26 weeks vs. placebo. Canagliflozin 300 mg helped more patients achieve the ADA-recommended HbA1c goal of <7.0% than sitagliptin 100 mg over 52 weeks.[5] In patients tolerating the starting dose of canagliflozin 100 mg once daily who have an eGFR of ≥60 mL/min/1.73 m^2 and require additional glycemic control, the dose can be increased to 300 mg once daily. Canagliflozin 300 mg helped more patients achieve the ADA-recommended HbA1c goal of <7.0% than glimepiride over 52 weeks. The dose of canagliflozin is limited to 100 mg once daily in patients with moderate renal impairment with an eGFR of 45 to <60 mL/min/1.73 m^2. It should not be initiated in patients with eGFR <45 mL/min/1.73 m^2. At 26 weeks, canagliflozin monotherapy provided statistically significant weight reductions vs. placebo, though it is indicated for weight loss. Furthermore, at 26 weeks, canagliflozin monotherapy provided statistically significant systolic blood pressure reductions versus placebo.

Adverse reactions

The most commonly reported adverse reactions (≥5%) were female genital mycotic infection, urinary tract infection, and increased urination.[6] Less commonly noted adverse effects (≤5% but more than 1.5%) includes male genital

mycotic infection, vulvovaginal pruritus, thirst, constipation and nausea. Patients may also experience dizziness or fainting, especially in the first 3 months of therapy, because canagliflozin is associated with a diuretic effect, which can reduce intravascular volume, leading to orthostatic or postural hypotension.

Drug interactions

Co-administration of canagliflozin with rifampin, a nonselective inducer of several UDP-glucuronyl transferase (UGT) enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (e.g., rifampin, phenytoin, and phenobarbital) must be co-administered with canagliflozin, consider increasing the dose to 300 mg once daily if patients are currently tolerating canagliflozin 100 mg once daily, have an eGFR >60 mL/min/1.73 m^2, and require additional glycemic control.

Warning and precautions

Orthostatic hypotension has been noted with canagliflozin and thus patients' volume status should be assessed and corrected, as necessary, before and during treatment. The use of canagliflozin in combination with insulin therapy or an insulin secretagogue (e.g., sulfonylureas) was associated with a higher incidence of hypoglycemia and may require a lower dose of insulin or an insulin secretagogue to reduce the risk of hypoglycemia. Dose-related increase in LDL-C is noted with canagliflozin in four 26-week placebo-controlled trials.[2]

Contraindication

Other than history of hypersensitivity reactions to canagliflozin, it should not be initiated in patients with severe renal function impairment (eGFR of less than 30 mL/min/1.73 m^2), with end-stage renal disease, or receiving dialysis. Canagliflozin is not expected to be effective in these patient populations

Use in special populations

There are no adequate and well-controlled studies of canagliflozin in pregnant women and nursing mothers. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with canagliflozin (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300-mg daily dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were ≥75 years of age.

CONCLUSIONS

The newly licensed novel glucose-lowering drug canagliflozin (*Invokana*, Janssen Pharmaceuticals) is a welcome addition to the armamentarium of treatment for type 2 diabetes mellitus. Canagliflozin, SGLT2 inhibitor, is a new class of oral drugs indicated only for the treatment of type 2 diabetes mellitus in conjunction with exercise and a healthy diet. Canagliflozin offer a novel insulin-independent approach for the control of hyperglycemia without incurring hypoglycemia. Their efficacy is not affected by the extent of insulin resistance or beta-cell dysfunction and, therefore, in principle, they can be used at any stage in the natural history of type 2 diabetes mellitus. Initial studies suggest they can be used as monotherapy or in combination with sulfonylureas, sitagliptin and insulin. Treatment is associated with a mean weight loss and a small reduction in blood pressure, which also may appear beneficial to patients with coexisting CVD, but further clinical trial results regarding long-term cardiovascular outcomes are needed to confirm the same.

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