Overview of Ertugliflozin
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Introduction
Despite the availability of 12 different classes of medications, many people with type 2 diabetes struggle to maintain glycemic control (1). Among the many new antidiabetic medications to have emerged in recent years, sodium–glucose cotransporter 2 (SGLT2) inhibitors have proved to be a particularly effective oral treatment for these patients (2). Since the approval of the first drug in this class, canagliflozin, by the U.S. Food and Drug Administration (FDA) in March 2013, a total of four SGLT2 agents have become available (both as single and fixed-dose combination formulas) (1). In 2017, an estimated 1.7 million patients received a dispensed prescription for an SGLT2 inhibitor from U.S. outpatient retail pharmacies (2). Ertugliflozin is the newest agent among these, having received FDA approval in December 2017. (3).

Indications
Ertugliflozin is indicated as an adjunct to diet and exercise for control of hyperglycemia in adults (≥18 years of age) with type 2 diabetes (4). It can be used as monotherapy in patients for whom metformin is contraindicated or not well tolerated. It can also be used in combination with other antidiabetic agents (most commonly metformin or a dipeptidyl peptidase-4 [DPP-4] inhibitor) to help reduce A1C. Currently, ertugliflozin is available as oral tablet sold under the brand name Steglatro or in oral tablet combinations with the DPP-4 sitagliptin (brand name Stegjuan) or with metformin (brand name Segluromet). Ertugliflozin is not approved for the treatment of type 1 diabetes, renal impairment, or ketoacidosis.

Mechanism of Action
As other SGLT2 inhibitors, ertugliflozin works by blocking glucose transport from the glomerular filtrate across the apical membrane of the proximal epithelial cells, resulting in increased urinary glucose excretion and reduced filtered glucose renal reabsorption. Ertugliflozin is predominantly metabolized by the enzymes UGT1A9 and UGT2B, with minor contributions by CYP3A4, and even less by CYP3A5 and CYP2C8 (4). Ertugliflozin does not inhibit CYP450 isoenzymes (CYPs) 1A2, 2C9, 2C19, 2C8, 2B6, 2D6, or 3A4 and does not induce CYPs 1A2, 2B6, or 3A4 (4). This might be beneficial in patients with type 2 diabetes who have complications and are on multiple medications because taking ertugliflozin would reduce the chance of having major interactions with drugs that are metabolized by these common enzymes (2).

Potential Advantages
Ertugliflozin has been shown to lower A1C in adults with type 2 diabetes. It has been studied extensively in multiple clinical trial settings and has been found to be effective in all of them (5). Three multicenter, randomized, double-blind, placebo- and active comparator-controlled clinical studies

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evaluating ertugliflozin have demonstrated its efficacy in further lowering A1C when used in combination with sitagliptin in 1,985 people with type 2 diabetes from different ethnic groups (6). Another phase 3 trial in 4,800 people with type 2 diabetes and moderate renal failure compared the use of ertugliflozin as monotherapy and in combination with metformin or sitagliptin, as well as insulin and a sulfonylurea. Results confirmed significantly lower A1C in those who took ertugliflozin alone or in combination with sitagliptin (6).

Ertugliflozin therapy may also be beneficial for patients who are overweight or hypertensive. Due to its mechanism of action, ertugliflozin induces more excretion of sodium through osmotic diuresis, which then leads to a mild reduction in blood pressure. Excretion of glucose in the urine also helps with weight loss due to loss of calories (7). Another study of ertugliflozin has shown it to be associated with a mean reduction in body weight of 6.6 lb with the 5-mg dose compared to 2.2 lb with placebo (7). More data are being collected to compare these benefits to those of other SGLT2 inhibitors.

Potential Disadvantages
Clinical trials have demonstrated that the safety profile of ertugliflozin is similar to other compounds in its class (i.e., association with genital mycotic infection, lower-limb amputation, urinary tract infection, acute kidney injury hypotension, and ketoacidosis) (5). Because this drug has been approved recently, data used to evaluate its associated risks with regard to these adverse effects are still being collected and will be updated in the near future (5). However, one could expect to see a range of adverse effects with ertugliflozin similar to those of other SGLT2 inhibitors.

A recent safety announcement from the FDA (1) has raised concern regarding the risk of Fournier’s gangrene, a rare but life-threatening bacterial infection of the genial areas, in patients taking an SGLT2 inhibitor. Twelve cases of have been identified since 2013 in both male and female patients who were being treated with an SGLT2 inhibitor (1). Ertugliflozin has included this information in its package insert, and patients being treated with this medication will be monitored closely in its post-marketing surveillance.

Cost
The out-of-pocket price of ertugliflozin in monotherapy tablets is $321.99 per 30-tablet bottle for 1 month of use based on recommended dosing (6). Currently, Merck has a copayment assistance program that will help cover some of patients’ out-of-pocket cost if private insurance is used to fill a prescription for ertugliflozin or its combination formulations with sitagliptin or metformin.

Commentary
Given its risk/benefit profile, ertugliflozin is considered a favorable drug of choice within the SGLT2 inhibitor class of medications. It does not contain a black box warning, as does canagliflozin for its risk of lower-limb amputation in people with type 2 diabetes and established cardiovascular disease (CVD) (8). However, prescribers must still consider carefully before starting this therapy in elderly patients with renal impairment and CVD, those with recurrent infections and high risk of limb amputation, and female patients with recurrent urinary tract infections.

Patient education is key before starting this therapy. The FDA released a safety announcement in August 2018 to advise patients treated with SGLT2 inhibitors to seek medical attention immediately if they experience symptoms of redness, swelling, or tenderness of the genital areas accompanied by a fever (8).

Bottom Line
Ertugliflozin seems to be a reasonable second- or third-line therapeutic option adjuvant to diet and exercise for people with type 2 diabetes who have not achieved their glycemic goals. Patients’ medical history, costs, and risk/benefit factors are key issues that should be thoroughly considered before starting patients on ertugliflozin therapy.

Duality of Interest
J.R.W. serves on an advisory board for Sanofi. No other potential conflicts of interest relevant to this article were reported.

Author Contributions
Both authors contributed to and were involved in the research, writing, and editing of this article. J.R.W. is the guarantor of this work and, as such, had full access to all of the references cited and takes responsibility for the accuracy of the content.

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