Jardiance (Empagliflozin), an SGLT2 Inhibitor, Receives FDA Approval for the Treatment of Patients with Type 2 Diabetes

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Diabetes is on the rise at an alarming rate in the United States. An estimated 9.3% of the US population, or 29.1 million people, are affected by diabetes.[1] Furthermore, approximately 37% of all US adults (51% of people aged ≥65 years) have prediabetes, a condition that greatly increases their risk for developing diabetes.[1] The prevalence of diabetes is projected to increase from 1 in 10 adults today to 1 in 3 adults by 2050, based on current trends and the aging of the population over the next few decades.[2] Type 2 diabetes mellitus, a type of diabetes characterized by insulin resistance and the gradual decline in the ability of the pancreas to produce insulin, accounts for an estimated 90% to 95% of all cases of diabetes.[1]

Associated with serious comorbidities, diabetes is the seventh leading cause of mortality and a major cause of stroke, heart disease, kidney failure, blindness, and other conditions.[1] Moreover, diabetes is associated with microvascular, macrovascular, and neuropathic complications that impact health and quality of life.[1]

The annual healthcare costs attributable to diabetes in the United States totaled $245 billion in 2012, including $176 billion in direct medical costs and $69 billion in indirect costs (ie, absenteeism, reduced or lost productivity, and disability).[3] Overall, the medical costs for people with diabetes are more than twice as high as costs for people without diabetes, and more than 1 in 5 US healthcare dollars is spent on diabetes care.[3]

Diabetes management is complex, requiring multiple considerations beyond glycemic control.[4] Approaches include incorporating lifestyle changes and self-management, providing appropriate education, minimizing the risk of weight gain, minimizing the risk of hypoglycemia, and targeting the patient's hemoglobin (Hb) A_{1c} goal on an individual basis, which is based on factors such as age, comorbid conditions, disease duration, adherence, and others.[5] Patients must be monitored on an ongoing basis, and the effectiveness of their therapies must be evaluated until stable results are achieved.[5]

Improvements in glycemic control are associated with improved outcomes for patients with type 2 diabetes. Lowering the HbA_{1c} level to ≤7% in appropriate patients is associated with a reduction in diabetes-related microvascular complications (ie, diabetic neuropathy, nephropathy, and retinopathy).[6] Pharmacologic treatments include metformin, sulfonylureas, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, insulin, and sodium glucose cotransporter-2 (SGLT2) inhibitors—the most recent class of antidiabetic agents.[7]

SGLT2 Inhibitors: The Newest Diabetes Drug Class

The kidney, which plays a key role in maintaining glucose homeostasis, has emerged as a therapeutic target in the treatment of type 2 diabetes.[8,9] In hyperglycemia, excess glucose is reabsorbed by the kidney, a process that increases the renal glucose threshold and creates a cycle of chronic hyperglycemia.[8,10] The SGLT2, located in the proximal tubule of the kidney, is responsible for reabsorbing 90% of renal glucose.[8] Inhibition of the SGLT2 reduces glucose reabsorption and lowers the renal threshold for glucose, leading to increased urinary glucose excretion and improved glycemic control.[8,10] The SGLT2 inhibitors may have a promising role, combined with diet and exercise, in improving glycemic control in patients with type 2 diabetes.

Empagliflozin: Another Option for Type 2 Diabetes

On August 1, 2014, empagliflozin (Jardiance; Boehringer Ingelheim), an SGLT2 inhibitor, was approved by the US Food and Drug Administration (FDA) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[11] Empagliflozin is an oral tablet taken once daily.[11] Empagliflozin is not indicated for the treatment of patients with type 1 diabetes mellitus or with diabetic ketoacidosis.[12]

According to Curtis J. Rosebraugh, MD, MPH, Director of the Office of Drug Evaluation II in the FDA's Center for Drug Evaluation and Research, "Jardiance provides an additional treatment option for the care of patients with type 2 diabetes. It can be used alone or added to existing treatment regimens to control blood sugar levels in the overall management of diabetes."[11]

Several postmarketing studies have been required by the FDA for empagliflozin, including the completion of an ongoing cardiovascular outcomes trial, a pediatric pharmacokinetic and pharmacodynamic study, a pediat-

ric safety and efficacy study, and a nonclinical (animal) juvenile toxicity study with a particular focus on renal development, bone development, and growth.[11]

Mechanism of Action

Empagliflozin is an inhibitor of SGLT2, the predominant transporter responsible for the reabsorption of glucose from the glomerular filtrate back into the circulation. By inhibiting SGLT2, empagliflozin reduces the renal reabsorption of filtered glucose and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion.[12]

Dosage and Administration

The recommended dose of empagliflozin is 10 mg once daily, taken in the morning, with or without food. This dose may be increased to 25 mg once daily.[12]

Before initiating therapy with empagliflozin, renal function should be assessed. Treatment with empagliflozin should be discontinued if the estimated glomerular filtration rate (eGFR) falls persistently below 45 mL/min/1.73 m^2.[12]

Empagliflozin is available in 10-mg and 25-mg tablets.[12]

Clinical Studies

Empagliflozin has been studied as monotherapy and in combination with metformin, sulfonylurea, pioglitazone, and insulin. In addition, empagliflozin has been studied in patients with type 2 diabetes mellitus with mild or moderate renal impairment.[12] Based on these studies, treatment with empagliflozin was shown to reduce HbA_{1c} compared with placebo in patients with type 2 diabetes.[12]

Empagliflozin Monotherapy: EMPA-REGMONO

In the EMPA-REGMONO trial, a total of 986 patients with type 2 diabetes participated in this double-blind, placebo-controlled study to evaluate the efficacy and safety of monotherapy with empagliflozin.[13]

Treatment-naïve patients with inadequately controlled type 2 diabetes entered an open-label placebo run-in phase for 2 weeks. At the end of the run-in period, patients who were still inadequately controlled and had an HbA_{1c} level between 7% and 10% were randomized to placebo, empagliflozin 10 mg, empagliflozin 25 mg, or a reference comparator.[12,13]

The results of this study are shown in **Table 1**. At week 24, monotherapy with empagliflozin 10 mg or 25 mg daily provided significant reductions in HbA_{1c} (P <.001), fasting plasma glucose (FPG), and body weight compared with placebo.[12,13]

Add-On Combination Therapy with Metformin: The EMPA-REG MET Trial

A total of 637 patients with type 2 diabetes participat-

Table 1 Empagliflozin Monotherapy versus Placebo: Results from the EMPA-REGMONO Trial at Week 24

Efficacy results	Empagliflozin 10 mg (N = 224)	Empagliflozin 25 mg (N = 224)	Placebo (N = 228)
HbA_{1c} level[a]			
Baseline, mean, %	7.9	7.9	7.9
Change from baseline, adjusted mean, %	–0.7	–0.8	0.1
Difference from placebo, adjusted mean, %	–0.7 (97.5% CI, –0.9 to –0.6)	–0.9 (97.5% CI, –1.0 to –0.7)	—
Patients achieving an HbA_{1c} <7%, N (%)	72 (35)	88 (44)	25 (12)
Fasting plasma glucose[b]			
Baseline, mean, mg/dL	153	153	155
Change from baseline, adjusted mean, mg/dL	–19	–25	12
Difference from placebo, adjusted mean, mg/dL	–31 (95% CI, –37 to –26)	–36 (95% CI, –42 to –31)	—
Body weight			
Baseline, mean, kg	78	78	78
Change from baseline, adjusted mean, %	–2.8	–3.2	–0.4
Difference from placebo, adjusted mean, kg	–2.5 (95% CI, –3.1 to –1.9)	–2.8 (95% CI, –3.4 to –2.2)	—

[a]Modified intent-to-treat population.
[b]N = 223 for empagliflozin 10 mg, N = 223 for empagliflozin 25 mg, and N = 226 for placebo.
CI indicates confidence interval; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin.
Sources: Jardiance (empagliflozin) tablets prescribing information; August 2014; Roden M, et al; for the EMPA-REGMONO Trial Investigators. *Lancet Diabetes Endocrinol.* 2013;1:208-219.

Table 2 Empagliflozin in Combination with Metformin versus Placebo plus Metformin: Results from the EMPA-REG MET Trial at Week 24

Efficacy results	Empagliflozin 10 mg + metformin (N = 217)	Empagliflozin 25 mg + metformin (N = 213)	Placebo (N = 207)
HbA_{1c} level[a]			
Baseline, mean, %	7.9	7.9	7.9
Change from baseline, adjusted mean, %	–0.7	–0.8	–0.1
Difference from placebo plus metformin, adjusted mean, %	–0.6 (97.5% CI, –0.7 to –0.4)	–0.6 (97.5% CI, –0.8 to –0.5)	—
Patients achieving an HbA_{1c} <7%, N (%)	75 (38)	74 (39)	23 (13)
Fasting plasma glucose[b]			
Baseline, mean, mg/dL	155	149	156
Change from baseline, adjusted mean, mg/dL	–20	–22	6
Difference from placebo, adjusted mean, mg/dL	–26	–29	—
Body weight			
Baseline, mean, kg	82	82	80
Change from baseline, adjusted mean, %	–2.5	–2.9	–0.5
Difference from placebo, adjusted mean, kg	–2.0 (95% CI, –2.6 to –1.4)	–2.5 (95% CI, –3.1 to –1.9)	—

[a]Modified intent-to-treat population.
[b]N = 216 for empagliflozin 10 mg, N = 213 for empagliflozin 25 mg, and N = 207 for placebo.
CI indicates confidence interval; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin.
Sources: Jardiance (empagliflozin) tablets prescribing information; August 2014; Häring H-U, et al; for the EMPA-REG MET Trial Investigators. *Diabetes Care*. 2014;37:1650-1659.

ed in the EMPA-REG MET trial, a placebo-controlled study to evaluate the efficacy and safety of empagliflozin in combination with metformin.[9] Patients with type 2 diabetes who were inadequately controlled with ≥1500 mg of metformin daily entered an open-label, 2-week, placebo run-in phase. At the end of the run-in period, patients who were still inadequately controlled and had an HbA_{1c} level between 7% and 10% were randomized to placebo, empagliflozin 10 mg, empagliflozin 25 mg, or a reference comparator.[9,12]

Findings from this study are shown in **Table 2**. At week 24, treatment with empagliflozin 10 mg or 25 mg daily demonstrated significant reductions in HbA_{1c} (P <.001), FPG, and body weight compared with placebo.[9,12]

Other Studies

Treatment with empagliflozin showed significant reductions in HbA_{1c} compared with placebo in several other clinical trials, including in combination with metformin and sulfonylurea; as add-on combination therapy with pioglitazone (with or without metformin); as add-on combination therapy with insulin (with or without metformin and/or sulfonylureas); and in patients with type 2 diabetes and renal impairment.[12] In addition, empagliflozin 25 mg was shown to be noninferior to glimepiride (at week 52) at lowering HbA_{1c} and FPG levels in an active controlled study versus glimepiride in combination with metformin.[12]

Safety

In clinical trials, the most common adverse reactions associated with empagliflozin 10 mg (≥5% incidence) were urinary tract infections (9.3%) and female genital mycotic infections (5.4%).[12] The most common adverse reactions associated with empagliflozin 25 mg (≥5% incidence) were urinary tract infections (7.6%) and female genital mycotic infections (6.4%).[12]

Discontinuation from clinical studies as a result of genital infection occurred in none of the patients receiving placebo and in 0.2% of patients receiving either empagliflozin 10 mg or 25 mg. The rates of treatment discontinuation as a result of urinary tract infections were 0.1%, 0.2%, and 0.1% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.[12]

Contraindications

The use of empagliflozin is contraindicated in patients with a history of serious hypersensitivity reaction to empagliflozin and in patients with severe renal impairment, end-stage renal disease, or those on dialysis.[12]

Warnings and Precautions

Hypotension. Empagliflozin causes intravascular volume contraction. Before initiating treatment with empagliflozin, volume status should be assessed and corrected in patients with renal impairment, in the elderly, in patients with low systolic blood pressure, and in patients receiving diuretics. Patients should also be monitored for the signs and symptoms of hypotension during therapy.[12]

Impairment in renal function. Empagliflozin increases serum creatinine and decreases eGFR. Renal function should be monitored during therapy. More frequent monitoring is recommended in patients with an eGFR <60 mL/min/1.73 m^2.[12]

Hypoglycemia. Insulin and insulin secretagogues are known to cause hypoglycemia. The risk for hypoglycemia is increased when empagliflozin is used in combination with insulin secretagogues (eg, sulfonylurea) or insulin. Consideration should be given to lowering the dose of insulin secretagogue or insulin to reduce the risk for hypoglycemia when initiating empagliflozin therapy.[12]

Genital mycotic infections. Empagliflozin increases the risk for genital mycotic infections. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop mycotic genital infections. Patients should be monitored and treated as appropriate.[12]

Urinary tract infections. Empagliflozin increases the risk for urinary tract infections. Patients should be monitored and treated as appropriate.[12]

Increased low-density lipoprotein cholesterol. Increases in low-density lipoprotein cholesterol can occur with empagliflozin. Patients should be monitored.[12]

Macrovascular outcomes. There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with empagliflozin.[12]

Use in Specific Populations

Pregnancy. There are no adequate and well-controlled studies in pregnant women. Empagliflozin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.[12]

Nursing mothers. Empagliflozin should be discontinued in nursing mothers or nursing should be discontinued.[12]

Geriatric patients. In geriatric patients aged ≥75 years, there was a higher incidence of adverse reactions related to volume depletion and reduced renal function and a higher risk for urinary tract infections.[12]

Renal impairment. In patients with renal impairment, there was a higher incidence of adverse reactions related to reduced renal function.[12]

Hepatic impairment. Empagliflozin may be used in patients with hepatic impairment.[12]

Conclusion

The FDA approval of empagliflozin in August 2014 provides another treatment option for patients with type 2 diabetes as an adjunct to diet and exercise. Empagliflozin, an SGLT2 inhibitor, improves glycemic control by blocking the reabsorption of glucose by the kidney, increasing glucose secretion, and lowering blood glucose levels in patients with type 2 diabetes.

Treatment with empagliflozin provided significant reductions in HbA_{1c} levels compared with placebo across multiple studies—as monotherapy, combined with metformin, as add-on combination therapy with metformin and sulfonylurea, as add-on combination therapy with pioglitazone (with or without metformin), as add-on combination therapy with insulin (with or without metformin and/or sulfonylureas), in combination with insulin (with or without metformin and/or sulfonylureas), and in patients with type 2 diabetes and renal impairment.

The reduction in HbA_{1c} levels shown with empagliflozin versus placebo was observed across various subgroups, including sex, race, geographic region, baseline body mass index, and disease duration.[12] ■

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