Dapagliflozin (Farxiga) Tablets

Manufacturer: Bristol-Myers Squibb, Princeton, New Jersey, and AstraZeneca, Wilmington, Delaware

Date of Approval: January 8, 2014

Indication: To improve glycemic control, along with diet and exercise, in adults with type-2 diabetes.

Drug Class: Dapagliflozin is described chemically as D-glucitol,1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl][phenyl],(1S),-compounded with (2S)-1,2-propanediol, hydrate (1:1:1). The molecular weight of the drug is 502.98.

Uniqueness of Drug: Dapagliflozin inhibits subtype 2 of the sodium-glucose transport proteins (SGLT2), which is responsible for at least 90% of the glucose reabsorption in the kidney. Blocking this transporter causes blood glucose to be eliminated through the urine. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion.

Warnings and Precautions:

Hypotension. Dapagliflozin causes intravascular volume contraction. Symptomatic hypotension can occur after initiating dapagliflozin, particularly in patients with impaired renal function, elderly patients, or patients taking loop diuretics. Monitor for signs and symptoms of hypotension after initiating therapy.

Impairment in renal function. Dapagliflozin increases serum creatinine and decreases eGFR. Elderly patients and patients with impaired renal function may be more susceptible to these changes.

Hypoglycemia with concomitant use of insulin and insulin secretagogues. Insulin and insulin secretagogues are known to cause hypoglycemia. Dapagliflozin can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when other agents are used in combination with dapagliflozin.

Genital mycotic infections. Dapagliflozin increases the risk of genital mycotic infections.

Increases in low-density lipoprotein cholesterol (LDL-C). Increases in LDL-C occur with dapagliflozin. Monitor LDL-C and treat per standard of care after initiating dapagliflozin.

Bladder cancer. The FDA warns consumers that dapagliflozin is not recommended for patients with active bladder cancer. Those with a history of bladder cancer should talk with their physicians before using the diabetes drug.

Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with dapagliflozin or any other antidiabetic drug.

Dosage and Administration: One 5-mg or 10-mg film-coated tablet daily. The recommended starting dose of dapagliflozin is 5 mg once daily, taken in the morning, with or without food. In patients tolerating dapagliflozin 5 mg once daily who require additional glycemic control, the dose can be increased to 10 mg once daily.

Commentary: Type-2 diabetes affects more than 25 million people and accounts for more than 90 percent of diabetes cases diagnosed in the United States. Over time, high blood sugar levels can increase the risk for serious complications, including heart disease, blindness, and nerve and kidney damage. Controlling blood sugar levels is very important in the overall treatment and care of diabetes. Dapagliflozin provides an additional treatment option for millions of Americans with type-2 diabetes.

The FDA is requiring six postmarketing studies for dapagliflozin:

• a cardiovascular outcomes trial (CVOT) to evaluate the cardiovascular risk of dapagliflozin in patients with a high baseline risk of cardiovascular disease;
• a double-blind, randomized, controlled assessment of bladder cancer risk in patients enrolled in the CVOT;
• an animal study evaluating the role of dapagliflozin-induced urinary flow/rate and composition changes on bladder tumor promotion in rodents;
• two clinical trials to assess the pharmacokinetics, efficacy, and safety in pediatric patients; and
• an enhanced pharmacovigilance program to monitor reports of liver abnormalities and pregnancy outcomes.

Sources: www.hms.com, www.fda.gov

Trametinib (Mekinist) in combination with Dabrafenib (Tafinlar)

Manufacturer: GlaxoSmithKline, Research Triangle Park, North Carolina

Date of Approval: January 9, 2014

Indication: The FDA granted fast-track approval for trametinib tablets and dabrafenib capsules in combination for the treatment of advanced (late-stage) unresectable melanoma skin cancer.

Drug Class: Chemically, tramatinib is N-(3-{3-Cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-1(2H)-yl)phenyl)acetamide. It has a molecular mass of 615.39 g/mol.

Dabrafenib is N-[3-[2-aminoptyrimidin-4-yl]-2-tert-butyl-1,3-thiazol-4-yl]-2-fluorophenyl]-2,6-difluorobenzesulfonyamide with a molecular weight of 502.56.

Uniqueness of Drug: Trametinib and dabrafenib are used to block signaling in different sites of the same molecular pathway that promotes cancer cell growth. They are specifically indicated as a combination therapy for patients with melanoma whose tumors express gene mutations called BRAF V600E
and V600K. The BRAF protein is involved in the regulation of normal cell growth, but it is mutated in approximately half of melanomas arising from the skin.

**Warnings and Precautions:**

*New primary malignancies (cutaneous and non-cutaneous).* When dabrafenib was used in combination with trametinib at the recommended dose, the incidence of basal-cell carcinoma was increased. The incidence of basal-cell carcinoma was 9% (5/55) in patients receiving the combination compared with 2% (1/53) in patients receiving dabrafenib as a single agent. Dabrafenib results in an increased incidence of cutaneous squamous-cell carcinoma (cSCC), keratoacanthoma, and melanoma. Cutaneous squamous-cell carcinoma, including keratoacanthoma, occurred in 7% of patients receiving the combination and 19% of patients receiving dabrafenib as a single agent.

*Tumor promotion in wild-type BRAF melanoma.* In *vitro* experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in wild-type BRAF cells that are exposed to BRAF inhibitors.

**Hemorrhage.** Treatment with the combination resulted in an increased incidence and severity of hemorrhagic events: 16% (9/55) of patients treated with the combination compared with 2% (1/53) of patients treated with dabrafenib as a single agent. Intracranial hemorrhage was fatal in two patients (4%) receiving the combination.

**Venous thromboembolic events.** Treatment with the combination resulted in an increased incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE): 7% (4/55) of patients treated with the combination compared with none of the 53 patients treated with dabrafenib as a single agent. Pulmonary embolism was fatal in one patient (2%) receiving the combination.

**Cardiomyopathy.** When trametinib was used in combination with dabrafenib at the recommended dose, cardiomyopathy (defined as cardiac failure, left ventricular dysfunction, or decreased left ventricular ejection fraction [LV EF]) occurred in 9% of patients (5/55) treated with the combination and in none of the patients treated with dabrafenib as a single agent. Pulmonary embolism was fatal in one patient (2%) receiving the combination.

**Ocular toxicities.** Across clinical trials of trametinib, the incidence of retinal vein occlusion (RVO) was 0.2% (4/1,749). RVO may lead to macular edema, decreased visual function, neovascularization, and glaucoma. In the randomized phase 2 part of the phase 1/2 open-label study, 2% of patients (1/55) receiving trametinib in combination with dabrafenib developed retinal pigment epithelial detachment. Uveitis and iritis can occur; across clinical trials of the combination, uveitis occurred in 1% of patients (2/202).

**Interstitial lung disease (ILD).** In clinical trials of trametinib (N = 329) as a single agent, ILD or pneumonitis occurred in 2% of patients.

**Serious febrile drug reactions.** Serious febrile reactions and fever of any severity accompanied by hypotension, rigors or chills, dehydration, or renal failure can occur when trametinib is used in combination with dabrafenib. The incidence and severity of pyrexia are increased when trametinib is given with dabrafenib compared with dabrafenib alone. The incidence of fever (serious and nonserious) was 71% (39/55) in patients treated with the combination and 26% (14/53) in patients treated with dabrafenib as a single agent. Febrile reactions of any severity, accompanied by hypotension, rigors, or chills, occurred in 25% of patients (14/55) treated with the combination compared with 2% of patients (1/53) treated with dabrafenib as a single agent.

**Serious skin toxicity.** The incidence of any skin toxicities, the most common of which were rash, dermatitis aciform rash, palmar-plantar erythrodysesthesia syndrome, or erythema, was similar for patients receiving the combination (65% [36/55]) compared with patients receiving dabrafenib as a single agent (68% [36/53]). Across all clinical trials of the combination (N = 202), severe skin toxicity requiring hospitalization occurred in 2.5% of patients (5/202).

**Hyperglycemia.** Hyperglycemia can occur when trametinib is used in combination with dabrafenib. The incidence of grade 3 hyperglycemia based on laboratory values was 5% (3/55) in patients treated with the combination compared with 2% (1/53) in patients treated with dabrafenib as a single agent.

**Glucose-6-phosphate dehydrogenase deficiency.** Dabrafenib, which contains a sulfonamide moiety, confers a potential risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

**Embryofetal toxicity.** Dabrafenib and trametinib both can cause fetal harm when administered to a pregnant woman. Dabrafenib can also render hormonal contraceptives ineffective.

**Dosage and Administration:** The combination of orally administered trametinib and dabrafenib at the recommended dose is 150 mg of dabrafenib twice daily and 2 mg of trametinib once daily.

**Commentary:** Melanoma is the most aggressive type of skin cancer and is the leading cause of death from skin disease. In 2014, the American Cancer Society estimates, about 76,100 new cases of melanoma will be diagnosed in the United States and about 9,710 people will die from the disease. In May 2013, the FDA approved both drugs as single agents to treat patients with unresectable or metastatic melanoma.

Trametinib is a mitogen-activated extracellular kinase (MEK) inhibitor that blocks the activation of the protein-kinase B-raf (BRAF) pathway, thereby causing decreased cellular proliferation, cell cycle arrest, and increased apoptosis.

Dabrafenib is a selective BRAF inhibitor that blocks tumor cell growth through inhibition of some mutated forms of BRAF, including the BRAF V600 mutation. The FDA approved the combination of trametinib and dabrafenib under the agency’s accelerated approval program, which allows the FDA to approve a drug to treat a serious disease based on clinical data showing that the drug has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients. This program provides earlier patient access to promising new drugs while the company conducts confirmatory clinical trials. The FDA also reviewed this combination of drugs under the agency’s priority review because they demonstrated the potential to be a significant improvement in safety or effectiveness in the treatment of a serious condition.