Ivacaftor (Kalydeco) Tablets

Manufacturer: Vertex and the Cystic Fibrosis Association, Cambridge, Mass.

Indication: Ivacaftor is used for the treatment of cystic fibrosis (CF) in adults and children 6 years of age and older who have a G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This medication is not beneficial in CF patients with two copies of the F508del mutation in the CFTR gene, which is the most common mutation that results in CF. Ivacaftor is designated as an orphan drug because of the rarity of the G551D mutation.

Drug Class: Ivacaftor is a CFTR potentiator.

Uniqueness of Drug: Ivacaftor is the first drug to treat the underlying cause of CF, a genetic disease. The medication keeps the CFTR channels open, regulating salt balance in order to enable transportation of chloride ions across the cell membrane in CF patients.

Warnings and Precautions:

Transaminase elevations. Because the use of ivacaftor may be associated with elevated levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST), these levels should be evaluated before ivacaftor is started, every 3 months during the first year of treatment, and every year thereafter. If transaminase levels become elevated, patients should be closely monitored until the abnormalities resolve. Therapy should be interrupted if ALT or AST values exceed five times the upper limit of normal. After levels return to normal, the clinician should weigh the benefits and risks of restarting ivacaftor.

Concomitant use with cytochrome P450 (CYP) 3A inducers. The use of ivacaftor with strong CYP3A inducers, such as rifampin and St. John’s Wort, is not recommended. These substances may markedly reduce the efficacy of ivacaftor.

Adverse effects. Upper respiratory tract infections, headache, stomach ache, rash, diarrhea, and dizziness have been reported.

Pregnancy. Ivacaftor is a Pregnancy Category B drug. Caution is recommended when ivacaftor is prescribed for breastfeeding mothers. For patients with moderate or severe hepatic impairment, a reduced dose is recommended less frequently.

Renal impairment. Caution is recommended when ivacaftor is used in patients with severe renal impairment.

Dosage and Administration: Ivacaftor should be taken with a fat-containing food, such as eggs, butter, peanut butter, or pizza made with cheese. The usual dose is a 150-mg oral tablet every 12 hours for adults and children 6 years of age and older.

CYP3A inhibitors. When ivacaftor is co-administered with a strong CYP3A inhibitor (e.g., ketoconazole), the dose should be reduced to 150 mg twice weekly. When ivacaftor is co-administered with a moderate CYP3A inhibitor (e.g., fluconazole), the dose should be reduced to 150 mg once daily. Grapefruit products and Seville oranges should be avoided.

Renal impairment. Ivacaftor has not been studied in patients with renal impairment. For individuals with mild-to-moderate impairment, no dosage adjustments are required. Caution is advised if impairment is severe (a creatinine clearance below 30 mL/minute) or if the patient has end-stage renal disease.

Hepatic impairment. For patients with hepatic mild impairment (Child–Pugh Class A), no dosage adjustments are required. For moderate (Child–Pugh Class B) impairment, the dose should be reduced to 150 mg once daily. The dosage for patients with severe impairment (Child–Pugh Class C) has not been studied, but ivacaftor levels can be expected to be higher. Ivacaftor should be used with caution at a reduced dose of 150 mg once daily or less frequently.

Commentary: CF is the most common fatal genetic disease in Caucasians, with a prevalence of approximately 30,000 persons in the U.S. Of these individuals, approximately 4% (1,200 patients) have the G551D mutation.

CF affects the lungs and other organs and almost always leads to an early death. It is caused by mutations in a gene that encodes for a protein, called CFTR, that regulates chloride and water transport in the body. This defect in transport results in the formation of thick mucus that builds up in the lungs, digestive tract, and other parts of the body, leading to severe respiratory and digestive problems and other complications such as infections and diabetes.

Pulmonary exacerbations are the leading cause of hospitalizations for patients with CF and account for 50% of the annual medical costs associated with the disease.

Ivacaftor is effective only in patients with CF who have the G551D mutation. If a patient’s mutation status is not known, a genetic test for CF should be conducted to determine whether the G551D mutation is present.


Vismodegib (Erivedge) Capsules

Manufacturer: Genentech, South San Francisco, Calif.

Indication: Vismodegib is indicated for the treatment of adults with metastatic basal cell carcinoma (BCC), those with locally advanced BCC that has recurred following surgery, or patients who are not candidates for surgery or radiation.

Drug Class: Vismodegib is a hedgehog-signaling-pathway inhibitor. The chemical formula is 2-chloro-N-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide. The drug’s molecular weight is 421.30 g/mol.

Uniqueness of Drug: Vismodegib binds to and inhibits the Smoothened homolog (SMOH), or Protein Gx, a transmem-
braneprotein involved in hedgehog signal transduction.

**Boxed Warning:** Therapy with vismodegib can result in embryo–fetal death or severe birth defects, as this drug is embryotoxic and teratogenic in animals. Teratogenic effects have included severe midline defects, missing digits, and other irreversible malformations. A female patient’s pregnancy status should be verified before the initiation of treatment. Male and female patients should be advised of the risks to the fetus. Female patients should also be advised of the need for contraception, and male patients should be advised of the potential risk of exposure to the drug through semen.

**Warnings and Precautions:** Because of its mechanism of action, vismodegib can cause fetal harm in pregnant women. Vismodegib is teratogenic, embryotoxic, and fetotoxic in rats at maternal exposures lower than the human exposures at the recommended dose of 150 mg/day. In rats, malformations included craniofacial anomalies, an open perineum, and absent or fused digits. Fetal retardation was also observed.

Pregnancy status should be verified before therapy with vismodegib is initiated. Both male and female patients should be informed about the risks of embryo-fetal death and severe birth defects and the need for contraception during and after treatment. Men and women of reproductive age should be counseled in pregnancy prevention and planning.

If vismodegib is used during pregnancy or if a woman becomes pregnant while taking vismodegib, she should be apprised of the potential hazards to the fetus. Women who might have been exposed to vismodegib during pregnancy, either directly or through seminal fluid, should be encouraged to participate in Genentech’s pregnancy pharmacovigilance program.

Patients should not donate blood or blood products while they are taking vismodegib and for at least 7 months after their last dose.

**Dosage and Administration:** The recommended dose is one 150-mg capsule taken orally once daily until disease progression or until unacceptable toxicity. Vismodegib may be taken with or without food. The capsules should be swallowed whole and should not be opened or crushed. If a dose of vismodegib is missed, administration should be resumed with the next scheduled dose.

**Commentary:** Vismodegib is used to treat adults with metastatic BCC, the most common type of skin cancer. The drug’s approval was based on a study of 96 patients.

Risk factors for BCC include light, freckled skin; the presence of many moles; long-term sun exposure or multiple sunburns early in life; x-ray exposure or other forms of radiation; and a family history of close relatives with skin cancer. BCC grows slowly and is usually painless. It can appear as a skin bump or growth or as a sore that doesn’t heal, bleeds easily, or has a sunken area in the middle. It is most likely to appear on sun-exposed areas of the skin.

Vismodegib is intended for patients who are not candidates for surgery or radiation and for those whose cancer has spread. In the U.S., 2 million new cases of BCC are diagnosed every year. BCC is not usually fatal, and it can be effectively treated; however, in some instances, the cancer cells metastasize and do not respond to standard surgery. A boxed warning mentions a risk of fetal death or severe birth defects.

**Sources:** FDA; www.erivedge.com; San Francisco Chronicle, January 21, 2012, www.sfgate.com

**Linagliptin/Metformin HCl (Jentadueto) Tablets**

**Manufacturer:** Boehringer Ingelheim, Ridgefield, Conn., and Eli Lilly, Indianapolis, Ind.

**Indication:** The combination of linagliptin (Tradjenta, Boehringer Ingelheim/Eli Lilly) and metformin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type-2 diabetes mellitus when treatment with both drugs is appropriate. Jentadueto has not been studied in combination with insulin.

**Drug Class:** The tablets contain the dipeptidyl peptidase-4 (DPP-4) inhibitor linagliptin and the biguanide metformin.

**Uniqueness of Drug:** Jentadueto prevents the degradation of two incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), and it increases active incretin hormone levels. These actions promote the release of insulin in a glucose-dependent manner and decrease the circulating levels of glucagon. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of elevated blood glucose levels, and GLP-1 suppresses glucagon secretion from pancreatic alpha cells, thereby reducing hepatic glucose output.

**Boxed Warning:** Lactic acidosis is a rare but serious complication that can result from metformin accumulation. The risk increases with renal impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment, and acute congestive heart failure. The onset is often subtle, accompanied only by non-specific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate. If acidosis is suspected, Jentadueto should be discontinued and the patient should be hospitalized immediately.

**Warnings and Precautions:**

**Lactic acidosis.** This serious metabolic complication can result from metformin accumulation during treatment with Jentadueto. Lactic acidosis is fatal in approximately 50% of cases. It has been reported primarily in diabetic patients with significant renal impairment, often in patients with multiple concomitant medical or surgical problems and who are taking multiple medications.

Patients with congestive heart failure who require pharmacological management have an increased risk of lactic acidosis, particularly when renal hypoperfusion and hypoxemia are also present. The risk of lactic acidosis is increased with the degree of renal impairment and the patient’s age. The risk may be decreased by regular monitoring of renal function in patients taking metformin.

Careful monitoring of renal function is recommended for elderly patients. Metformin therapy should not be initiated in any patient if the creatinine clearance demonstrates that renal function is impaired. Metformin should be promptly withheld if the patient has any condition associated with hypoxemia, dehydration, or sepsis.

**Monitoring of renal function.** Before Jentadueto therapy is begun, and at least annually thereafter, renal function should be assessed and verified as normal. If renal impairment is
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anticipated, as in elderly patients for example, renal function should be assessed more frequently. Jentadueto should be discontinued if renal impairment is present; it should also be temporarily discontinued before any intravascular radiocontrast studies or surgical procedures that call for restricting the intake of food or fluids.

Impaired hepatic function. Liver injury has been associated with cases of lactic acidosis resulting from metformin therapy. Jentadueto tablets should generally be avoided in patients with hepatic impairment.

Hypoglycemia. Insulin secretagogues can cause hypoglycemia. In a clinical trial, the use of linagliptin in combination with an insulin secretagogue (e.g., a sulfonylurea) was associated with a higher rate of hypoglycemia compared with placebo. A lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when it is used with Jentadueto.

Vitamin B$_{12}$ levels. Metformin therapy may cause a decrease in vitamin B$_{12}$ levels. Hematological parameters should be monitored annually.

Alcohol intake. Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving Jentadueto.

Hypoxic states. Cardiovascular collapse (shock) from acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. If patients taking Jentadueto experience any of these events, the drug should be promptly discontinued.

Macrovascular outcomes. No clinical studies establishing evidence of macrovascular risk reduction with Jentadueto or any other antidiabetic drug have been conducted.

Dosage and Administration: Jentadueto tablets are taken twice daily, alone or in combination with a sulfonylurea, another commonly prescribed medication for type-2 diabetes.

Contraindications: Jentadueto should not be used to treat patients with type-1 diabetes, diabetic ketoacidosis, or kidney disease.

Commentary: The efficacy of linagliptin plus metformin was shown in a 24-week, randomized, controlled trial in adults with type-2 diabetes. Jentadueto was associated with reductions of up to 1.7% in glycosylated hemoglobin (HbA$_1c$). Although some diabetologists claim that the new combination tablet is merely a matter of convenience, many patients with type-2 diabetes require more than one medication to improve blood glucose levels because of the complex nature of the condition.