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Ivacaftor for the Treatment of Patients with Cystic Fibrosis and the G551D-CFTR Mutation

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On January 31, 2012, the Food and Drug Administration (FDA) approved ivacaftor (Kalydeco™, Vertex Pharmaceuticals, Inc., formerly known as VX-770) for the treatment of cystic fibrosis (CF) in patients 6 years of age and older who have the G551D mutation in the CF transmembrane regulator (CFTR) gene.[1,2] As the first drug to target the defective CFTR protein rather than treat symptoms, ivacaftor represents a significant breakthrough for patients with CF. This development also reflects the success of a long-term collaborative effort between the manufacturer, an established network of CF centers and academic research laboratories located throughout Europe, North America, and Australia, and Cystic Fibrosis Foundation Therapeutics, Inc., the drug development branch of the Cystic Fibrosis Foundation.[3,4]

Mechanism of Action

Ivacaftor, *N*-(2,4-di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide, is classified by the FDA as a CFTR potentiator. The CFTR protein is a chloride channel found in the surface of epithelial cells throughout the body. Mutation of the CFTR gene may result in a reduced number of CFTR channels at the apical surface, impaired channel function, or both.

The G551D-CFTR mutation results in defective channel opening, or gating, in response to cellular signals. It is estimated to be present in 4% of patients with CF, affecting approximately 1,200 people in the US. Ivacaftor facilitates increased chloride transport by potentiating open-channel probability of G551D-CFTR. In vitro studies utilizing CF human bronchial epithelial cells positive for G551D have shown that ivacaftor increases stimulated chloride secretion and also reduces excessive sodium and fluid absorption, preventing dehydration of the airway surface liquid and improving cilia motility.[2,3]

Ivacaftor is indicated for treatment of patients with at least one G551D-CFTR mutant allele.[2,3] A recent in vitro study suggests a possible role for ivacaftor in other CFTR gating mutations, including G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D.[5] Clinical trials have specifically demonstrated lack of efficacy of ivacaftor in patients homozygous for the F508del-CFTR mutation, which impairs cellular processing and delivery of CFTR to the epithelial cell surface. The F508del mutation is present in 90% of CF patients in North America. The manufacturer currently has a CFTR corrector compound (VX-809) in phase II studies for patients with the F508del-CFTR mutation.[6]

Pharmacokinetics

The pharmacokinetic profile of ivacaftor has been assessed in healthy adults and patients with CF, producing similar results. After an oral 150 mg dose in healthy, fed volunteers, the mean peak plasma concentration (±SD) was 768 ± 233 ng/mL, with an area under the concentration-time curve (AUC) of 10,600 ± 5,260 ng•hr/mL. The average time to peak concentration was approximately 4 hours. High-fat foods increase the bioavailability of ivacaftor 2-to 4-fold.[2]

Ivacaftor is highly protein bound (99%) to both albumin and alpha 1-acid glycoprotein. The mean apparent volume of distribution in healthy adults was 353 ± 122 L after a week of therapy. Ivacaftor undergoes hepatic metabolism, primarily via CYP3A4. Two of its metabolites, M1 and M6, possess pharmacologic activity ($1/6^{th}$ and $1/5^{th}$ the potency of the parent compound, respectively). The metabolites are eliminated in the feces; there is minimal renal elimination. The apparent clearance of ivacaftor in healthy volunteers given a single 150 mg dose was 17.3 ± 8.4 L/hr, with a terminal half-life of approximately 12 hours. Clearance is slowed in patients with hepatic impairment, necessitating a reduction in the frequency of dose administration.[2]

Clinical Studies

The FDA approved ivacaftor within three months of submission of the new drug application, under

the priority review program. The approval was based largely on the results of one proof of concept dose-ranging study conducted in 39 adults and two 48-week clinical studies which enrolled at total of 213 children and adults. Two of the studies have been published in *The New England Journal of Medicine*.[7,8]

In 2010, Accurso and colleagues published the results of a randomized, double-blind, cross-over dose-ranging study in 39 adults with CF and at least one G551D-CFTR allele.[7] Twenty subjects were randomized to receive ivacaftor at a dose of 25, 75, or 150 mg or placebo orally every 12 hours for 14 days in the first phase of the study. At day 14, the mean relative change from baseline in the percentage of predicted FEV_1 was 4.9% (95% CI -2.6, 12.5), 10% (95% CI 4.5, 15.6), and 10.5% (95% CI 3.3, 17.7) in the 25, 75, and 150 mg groups, respectively, with a 0.7% change (95% CI -8.8, 10.2) in the placebo group. The improvement was statistically significant only in the 75 mg and 150 mg groups ($p = 0.002$ and $p = 0.008$ for within-subject comparison with baseline values).

Based on the results of the first phase, another 19 subjects were randomized to an ivacaftor dose of 150 or 250 mg or placebo every 12 hours for 28 days. At completion of the study, the median relative change from baseline in the percentage of predicted FEV_1 was 8.7% (range 2.3-31.3%, $p = 0.008$) in the 150 mg group, 4.4% (0-18.3%, $p = 0.03$) in the 250 mg group, and 7.3% (4.2-8.2%, $p = 0.13$) in the controls. Combined data from the subjects receiving ivacaftor 150 mg every 12 hours revealed a median change in the nasal potential difference in response to an isoproterenol challenge of -3.5 mV (range -8.3 to 0.5 mV, $p = 0.02$ for within-subject comparison), demonstrating a positive effect on nasal electrophysiology. The median change in sweat chloride was -59.5 mmol/L (range -66.0 to -19.0; $p = 0.008$). Two subjects experienced a serious adverse reaction: a rash in one patient and 5 incidents of elevated blood or urine glucose levels in a patient with underlying diabetes. None of the subjects withdrew from the study. Based on the results of this brief dose-ranging study, the authors concluded that ivacaftor, at a dose of 150 mg every 12 hours, produced significant improvement in CFTR and lung function compared to baseline in patients with the G551D-CFTR mutation.

The following year, Ramsey and colleagues (writing for the VX08-770-102 Study Group) published the first of the 48-week efficacy trials.[8] A total of 161 subjects were enrolled in this phase III randomized, double-blind, placebo-controlled trial. Subjects ranged in age from 12 to 53 years (mean 31 years). All patients had at least one G551D-CFTR mutation. The subjects were randomized to either ivacaftor 150 mg or placebo every 12 hours, given with a high-fat meal. Results were based on assessments at weeks 24 and 48.

At 24 weeks, the change from baseline in predicted FEV_1 was significantly greater in the ivacaftor group (10.4 percentage points in the ivacaftor group versus -0.2 percentage points in the controls, $p < 0.0001$). The mean increase in FEV_1 was 0.367 L in the treatment group, compared to 0.006 L in the controls ($p < 0.001$), corresponding to a relative change from baseline of 17.2% with treatment and 0.1% with placebo. For most subjects, treatment effect was evident by the end of the second week. Response to treatment was sustained at week 48, with a change from baseline in predicted FEV_1 10.5 percentage points greater in the ivacaftor group ($p < 0.001$).

Sixty-seven percent of the subjects in the treatment group had remained free of pulmonary exacerbations at week 48 compared to 41% of the controls ($p = 0.001$). There were 99 exacerbations in the placebo group, but only 47 in the treatment group. Hospitalizations were less frequent in the ivacaftor group (21 in 11 patients) compared to the controls (31 in 23 patients). Mean change from baseline in scores for the respiratory domain of the CF Questionnaire-revised instrument was significantly greater in the ivacaftor group (a 5.9 point increase versus a 2.7 point decrease in the controls, $p < 0.001$). A change of 4 points on this scale is considered the threshold for clinical significance. Weight gain was also significantly greater in the treatment group (mean 3.1 kg versus 0.4 kg in the controls, $p < 0.001$), with a plateau after 16 weeks.

At week 24, the change from baseline in sweat chloride was -48.7 mmol/L in the ivacaftor group and – 0.8 mmol/L in the controls ($p < 0.001$). The mean value for sweat chloride in the ivacaftor group was 47.8 mmol/L, lower than the 60 mmol/L diagnostic threshold for CF. This treatment effect was noted in most subjects by day 15 and was sustained through week 48.

Serious adverse effects were identified in 20 ivacaftor patients (24%) and 33 controls (42%). In addition to pulmonary exacerbations, hemoptysis was reported in four controls and one patient receiving ivacaftor. Hypoglycemia was reported in two subjects in the ivacaftor group, including one subject with diabetes who was receiving insulin. Four subjects in the placebo

group and one in the ivacaftor group withdrew from the study because of an adverse effect.

A second randomized, double-blind, placebo-controlled efficacy trial was conducted in 52 children between 6 and 11 years of age (mean 9 years).[2] The results of this trial have not yet been published, but are available in the product prescribing information. Randomization was identical to the previous trial, with ivacaftor administered at a dose of 150 mg every 12 hours. As in the first efficacy trial, at 24 weeks the change from baseline in predicted FEV_1 was significantly greater in the ivacaftor group (12.5 percentage points greater than in the controls, $p < 0.0001$). This change persisted at 48 weeks. Weight gain was also significantly greater in the treatment group, with a mean absolute change from baseline of 1.9 kg (95% CI 0.9, 2.9) at week 24 and 2.8 kg (95% CI 1.3, 4.2) at week 48 ($p = 0.0004$ and $p = 0.0002$, respectively). The results of these trials provided strong support for the approval of ivacaftor in patients with the G551D-CFTR mutation.

Warnings and Precautions

Elevations in serum transaminases have been identified in patients receiving ivacaftor during clinical trials. The rates of AST or ALT elevation greater than 3, 5, or 8 times the upper limit of normal (ULN) were 6%, 3%, and 2% in the ivacaftor group and 8%, 2%, and 2% in the controls, respectively. The manufacturer recommends obtaining baseline AST and ALT values prior to starting therapy, followed by testing every 3 months for the first year of treatment and annually thereafter. Patients with transaminase elevations less than 5 times the ULN may continue on therapy, but should be closely monitored. Those with transaminase elevations 5 times the ULN or greater should discontinue ivacaftor treatment until levels return to baseline. Reintroduction of treatment may be considered at that time.[2]

Adverse Effects

The adverse effects of ivacaftor were assessed in a total of 353 adult and pediatric subjects with CF taking part in clinical trials. The most commonly reported reactions in the pooled data were headache (in 17% of patients), upper respiratory tract infection (16%), nasal congestion (16%), nausea (10%), rash (10%), rhinitis (6%), dizziness (5%), arthralgia (5%), and bacteria in sputum (5%). Other adverse effects reported at rates greater than placebo included oropharyngeal pain (24%), abdominal pain (16%), and diarrhea (13%).[2]

In the pooled clinical trial data, 2% of subjects receiving ivacaftor discontinued treatment because of adverse effects compared to 5% of subjects receiving placebo. Serious adverse effects reported with ivacaftor have included pulmonary exacerbations, hemoptysis, increased serum transaminases, abdominal pain, and hypoglycemia or hyperglycemia.[2]

Drug Interactions

Ivacaftor is a substrate for CYP3A4 and its clearance is altered by inducers or inhibitors of this enzyme. Strong CYP3A4 inducers, such as carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, or St. John's wort, can significantly increase the clearance of ivacaftor, potentially resulting in therapeutic failure. Concomitant use of these drugs with ivacaftor should be avoided.[2]

Administration of ketoconazole, a strong CYP3A4 inhibitor, can increase ivacaftor concentration more than eight-fold. The dose of ivacaftor should be reduced in patients requiring treatment with ketoconazole or other strong CYP3A4 inhibitors such as clarithromycin, erythromycin, itraconazole, posaconazole, telithromycin, or voriconazole. Patients receiving fluconazole or erythromycin, which are moderate CYP3A4 inhibitors, may experience up to a three-fold increase in ivacaftor concentrations. Dose reduction is also recommended for patients taking these agents (see Dosing Recommendations below). Ingestion of grapefruit, Seville oranges, orange marmalade, or grapefruit juice should be avoided, as these foods also inhibit CYP3A4.[2]

Ivacaftor and its M1 metabolite produce relatively weak inhibition of CYP3A4 and P-glycoprotein, but may have the potential to increase serum concentrations of drugs relying on these enzymes for clearance. Concentrations of midazolam have been shown to increase 1.5-fold in patients taking ivacaftor. Although no specific dosing adjustments are recommended, ivacaftor should be used with caution in patients receiving midazolam, digoxin, cyclosporine, or tacrolimus.[2]

Availability

Ivacaftor (Kalydeco™, Vertex Pharmaceuticals, Inc.) is available in 150 mg tablets.[2] The anticipated cost of therapy is $294,000 per year. The manufacturer has stated that the drug would be provided without charge to patients with a household income of $150,000 or less who do not have insurance.[9] For patients with insurance, Vertex will help to cover copay or coinsurance costs up to 30% of the cost of the drug. Vertex has developed a patient-assistance program, called Vertex GPS: Guidance & Patient Support, to assist patients with determining insurance

coverage or obtaining reimbursement support. Information on the program is available by calling 1-877-7KALYDECO (1-877-752-5933). The enrollment form is available at http://www.vertexgps.com/kalydeco/hcp/kalydeco-healthcare-professionals.

Dosing Recommendations

The recommended dose of ivacaftor in adults and children 6 years of age and older is 150 mg every 12 hours. The dose should be taken with high-fat foods to increase absorption. Examples include eggs, butter, peanut butter, or cheese pizza. Eating grapefruit or Seville oranges, or drinking their juices, should be avoided while taking ivacaftor. The dose of ivacaftor should be reduced to 150 mg once daily in patients with moderate hepatic impairment (Child-Pugh Class B). Ivacaftor should be used with caution in patients with severe hepatic impairment (Child-Pugh Class C), at a dose of no more than 150 mg once daily and with consideration of dosing even less frequently. Patients receiving concomitant therapy with a strong CYP3A4 inhibitor should receive ivacaftor 150 mg twice weekly, while patients taking a moderate CYP3A4 inhibitor should be treated with ivacaftor 150 mg once daily. No dose adjustment is needed for patients with mild to moderate renal impairment. Use of ivacaftor in patients with severe renal impairment has not been studied.[2]

Summary

Since the identification of the CFTR gene in 1989, there has been a focused effort on developing therapies to correct the defective gene or minimize its impact. Although this drug targets only 4% of the CF population, those with the G551D mutation, ivacaftor represents the first product approved by the FDA that improves defective CFTR function and ushers in a new era for the treatment of children and adults with CF. In addition to improved pulmonary function test results, ivacaftor has produced significant improvement in weight gain and patient assessment of respiratory symptoms. It has also led to fewer pulmonary exacerbations and a reduction in sweat chloride values to below the diagnostic threshold in many patients. Much more work is underway in this field, including trials of ivacaftor in children less than 6 years of age and studies of CFTR potentiators or correctors targeted at other mutations.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their March meeting:

1. Two pancrelipase products were added to the Formulary. Zenpep® is restricted to use by Pediatrics and Viokace™ is restricted to use in patients requiring enteral tube feedings.
2. Bosentan (Tracleer®) and ambrisentan (Letairis®) were added for use in patients already on therapy prior to admission.
3. Glucarpidase (Voraxaze®) was added to the Formulary for patients being treated with high-dose methotrexate regimens.
4. Palifermin (Kepivance®) was added with restriction to adult stem cell transplant patients.
5. Etonogestrel intradermal implant (Nexplanon®) was added to the Formulary for clinic use. The oral combination contraceptives were modified to include ethinyl estradiol 50 mcg/norgestrel 0.5 mg, ethinyl estradiol 35 mcg/levonorgestrel 0.1 mg, and ethinyl estradiol 35 mcg/norgestimate 0.25 mg.
6. Isradipine, methyltestosterone, and rosiglitazone were deleted.

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