## Ivacaftor: A Novel Gene-Based Therapeutic Approach for Cystic Fibrosis

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Ivacaftor is a new therapeutic agent that acts at the cystic fibrosis transmembrane conductance regulator (CFTR) channel to alter activity. It is approved for use in patients 6 years and older with cystic fibrosis who have at least 1 G551D mutation in the CFTR gene. It is unlike any other current pharmacologic agent for cystic fibrosis in that it specifically targets the gene defect associated with cystic fibrosis as opposed to treating resulting symptomology. Mucoactive agents, antibiotics, inhaled beta agonists, and other anti-inflammatory agents are currently the mainstay of cystic fibrosis treatment but can be associated with several side effects in addition to cumbersome frequency of administration. Ivacaftor's oral dosing regimen offers a more convenient treatment option. However, it is associated with significant drug-drug interactions.

INDEX TERMS cystic fibrosis, CFTR, ivacaftor

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#### INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive genetic disorder that affects chloride transport throughout the body's epithelial cells, resulting in abnormalities in the respiratory, endocrine, gastrointestinal, and reproductive systems. This life-shortening disease requires multiple daily medications to prolong life and improve quality of life. Each of these medications has an important role in addressing the symptoms of CF but, until recently, none have targeted the genetic defect that causes CF.

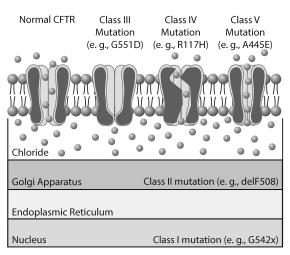
Ivacaftor (Vx-770; Kalydeco, Vertex Pharmaceuticals, Cambridge, MA) is a new and novel genebased therapy for the treatment of CF. The Food and Drug Administration (FDA) approved its label for use in patients age 6 years and older with CF who have at least 1 G551D mutation in the CF transmembrane conductance regulator (CFTR) gene.<sup>1</sup> It is the first of hopefully many agents that target the underlying gene defect in CF.

At least 5 classes of CF mutations have been identified to describe the more than 1900 identified CF-causing mutations. These are illustrated in Figure. CF mutations result mostly in impaired channel function at the cell surface, reduction in the number of CFTR channels at the cell surface, or both.<sup>2</sup> Class I defects cause truncated protein translation, while class II defects result in misfolded CFTR.<sup>3</sup> Both of these mutations result in impaired delivery of CFTR proteins to the cell surface. Class III and IV defects result in full-length CFTR that reach the cell surface but exhibit gating defects or reduced pore conductivity, respectively.<sup>3</sup> Class V defects reduce CFTR surface expression.<sup>3</sup>

The target CFTR-mutation of ivacaftor, G551D, is a Class III defect. The CFTR protein reaches the cell surface, but the ability of the channel to open is impaired.<sup>2</sup> This results in multi-organ dysfunction. The G551D phenotype is usually associated with pancreatic insufficiency.<sup>4</sup> By increasing the flow of ions through activated CFTR present at the cell surface, ivacaftor allows the opening probability of the channel to be increased.<sup>2</sup> Hence, ivacaftor is classified as a CFTR potentiator.

#### **MECHANISM OF ACTION**

Ivacaftor is an oral agent that increases ion-



**Figure.** Classes of CFTR mutations. Class I and II mutations result in CFTR protein that does not reach the cell surface due to impaired protein translation in the cell nucleus (Class I) or misfolded protein in the golgi apparatus (Class II). Class III and IV mutations result in CFTR that reaches the cell surface but exhibits impaired function due to a gating defect (Class III) or decrease conductivity (Class IV). Class V mutations lead to a reduced production of normal CFTR. CFTR, cystic fibrosis transmembrane conductance regulator.

function of activated cell-surface CFTR. *In vitro* studies using bronchial epithelial cells from the lungs of patients with CF have demonstrated that increases in the air-surface fluid level and ciliary beat frequency can be obtained by correction of abnormal CFTR-mediated ion transport.<sup>5</sup> Possible improvement in airway obstruction could occur by decreasing mucus plugging through better hydration of the airway surface and increased mucus clearance.<sup>5</sup>

## THERAPEUTIC EFFICACY

Three randomized controlled trials have been identified investigating the efficacy and safety of ivacaftor. The first study conducted by Accurso and colleagues<sup>6</sup> evaluated the safety and adverseevent profile of ivacaftor in patients age 18 years or older with at least 1 G551D mutation. Doses in 25, 75, or 150 mg were studied for 14 days followed by a dose of 150 or 250 mg for 28 days. It was concluded that ivacaftor was associated with few severe side effects. Although efficacy was not a primary end point, an 8.7% (range, 2.3–31.3) change in forced expiratory volume in 1 second (FEV<sub>1</sub>) from baseline was observed, and median sweat chloride decreased 59.5 mmol/L.

A second study conducted by Ramsey and colleagues<sup>5</sup> sought to evaluate the efficacy and safety of ivacaftor 150 mg twice daily for 48 weeks in 161 patients age 12 years or older with at least 1 G551D mutation. At 24 weeks, ivacaftor administered at this dose resulted in a 10.6% improvement in predicted FEV<sub>1</sub> from baseline versus placebo. A 55% reduction in the risk of pulmonary exacerbations was observed. Mean values for sweat chloride at 24 weeks were 47.8 mmol/L in the ivacaftor group versus 100.0 mmol/L in the placebo group.<sup>5</sup> Cystic Fibrosis Questionnaire-Revised respiratory domain scores increased by 5.9 points versus 2.7 points in the placebo group by week 48 signifying improved quality of life. Patients in the ivacaftor group also gained 3.1 kg, which was also statistically significant when compared to placebo. In regards to safety, elevated hepatic enzyme levels led to discontinuation of ivacaftor in 1 subject.

The studies in children 6 to 12 years of age are currently unpublished, but a 48-week study is reported to have included 52 patients and resulted in a 12.5% improvement in FEV<sub>1</sub> and 2.8 kg weight gain compared to placebo.<sup>1</sup> Additionally, a decrease in mean sweat chloride of 54 mmol/L was observed.

Flume and colleagues<sup>7</sup> evaluated the safety of ivacaftor 150 mg twice daily for 96 weeks in patients age 12 years or older with homozygous delta F508 CFTR mutations. Similar adverse events were reported between ivacaftor and placebo. However, lack of clinical efficacy supports the idea that ivacaftor alone is not sufficient in patients without a gating defect.

A phase II randomized, double-blind, placebocontrolled study including patients 18 years or older with 2 copies of delta F508 combined Vx-809 (a F508del corrector) and ivacaftor (250 mg every 12 hours). From Day 28 to 56, a mean absolute improvement in lung function of 6.1% within the group was observed. A mean absolute improvement in lung function of 8.6% was observed when compared to placebo.<sup>8</sup>

At this time, ivacaftor has only been studied as adjunct therapy to standard of care. In clinical trials, patients remained on their prestudy medications. Use of CYP 3A4 inhibitors, inducers, and inhaled hypertonic saline were prohibited.

#### PHARMACOKINETICS

In regards to absorption, ivacaftor is best

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absorbed if given with a high-fat meal, and in its presence, ivacaftor's exposure increases up to fourfold.<sup>1</sup> Peak plasma concentrations are achieved at approximately 4 hours postdose.<sup>1</sup> After twice daily dosing, steady state plasma concentrations are reached by an average of 3 to 5 days.<sup>1</sup>

Ivacaftor is 99% plasma protein bound, mainly to albumin and alpha 1-acid glycoprotein, which leads to potential drug interactions with unknown clinical significance.<sup>1</sup> Mean apparent volume of distribution was 353 L after administration of 1 week of 150 mg twice daily.<sup>1</sup>

Ivacaftor is extensively metabolized by the liver primarily by CYP3A. Two major metabolites, M1 and M6, are produced.<sup>1</sup> M1 is pharmacologically active and retains about one-sixth the potency of the parent drug.<sup>1</sup> M6 is not pharmacologically active as it retains less than one-fiftieth the potency of the parent drug.<sup>1</sup> Patients who exhibit hepatic impairment may require an adjustment in dosing frequency.<sup>1</sup> No dose adjustments are required for patients with mild hepatic impairment (Child-Pugh Class A). The recommended dose for moderately hepatic impaired patients (Child-Pugh Class B) is 150 mg once daily or less often in patients with severe hepatic impairment (Child-Pugh Class C).

Approximately 88% of ivacaftor is excreted in the feces. Major metabolites, M1 and M6, account for over half of the total dose eliminated as 22% and 43% are excreted, respectively. Renal excretion of unchanged parent drug is minimal; therefore, no dose adjustments are recommended for patients with mild to moderate renal impairment. Although ivacaftor has not been studied in patients with any degree of renal impairment, caution is recommended in patients with severe renal impairment or endstage renal disease.<sup>1</sup>

#### DOSING

Ivacaftor is available as 150 mg tablets and approved for patients with CF age 6 and older who possess at least 1 G551D mutation in the CFTR gene.<sup>1</sup> The initial dose is 150 mg orally every 12 hours for both the adult and pediatric population.<sup>1</sup> Dosage adjustments are necessary if ivacaftor is administered with moderate or strong CYP3A inhibitors, 150 mg once daily and 150 mg twice weekly, respectively.<sup>1</sup>

## CARCINOGENICITY, TERATOGENICITY, AND EXCRETION IN BREAST MILK

In studies using rats and mice, no evidence of tumorigenicity was observed. Impaired fertility and reproductive indices were found in male and female rats at doses of 200 mg/kg/day. Also noted was an increased number of female rats with nonviable embryos as well as decreased corpora lutea, viable embryos, and implantations at the aforementioned dose. These impairments are attributed to severe toxicity as none were observed at doses less than or equal to 100 mg/kg/day.<sup>1</sup> Ivacaftor is FDA pregnancy risk category B as there are no well-controlled or adequate studies in pregnant women. Thus, ivacaftor should only be used during pregnancy if benefits outweigh risks and on a highly individualized patientspecific case-by-case basis.<sup>1</sup>

Studies in lactating rats show that ivacaftor is excreted into their milk. Currently there is no data available on human breast milk excretion and caution should be exercised if administered to nursing women.<sup>1</sup>

#### SIDE EFFECTS

The most common adverse effects in clinical trials included headache, upper respiratory tract infection, nasal congestion, rash, and dizziness.5,6 Incidence of adverse effects were similar to placebo with fewer serious adverse effects leading to discontinuation occurring in the ivacaftor group than with placebo.5 The only adverse event experienced by 1 patient leading to discontinuation in the ivacaftor group was increased hepatic enzyme levels,5 hence the recommendation to monitor liver function tests every 3 months for the first year of therapy and subsequently once a year. Interruption of therapy is warranted in patients with an aspartate aminotransferase or alanine transaminase greater than 5 times the upper limit of normal. Clinicians should consider the risks versus benefits prior to resuming ivacaftor once hepatic enzymes return to baseline.1

#### **DRUG INTERACTIONS**

Ivacaftor exhibits multiple mechanisms by which drug interactions occur, one of which is cytochrome P450 isoenzymes. Ivacaftor is a sensitive CPY3A substrate.<sup>1</sup> Therefore, co-administra-

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#### Table 1. Drug Interactions and Dose Adjustments

<b>Co-administered Medication</b>	<b>CYP</b> Interaction	Recommendation
Midazolam, alprazolam, diazepam, triazolam	3A substrate	Use with caution and monitor benzodiazepine-related side effects
Rosiglitazone	2C substrate	No dose adjustments necessary
Warfarin	2C9 substrate	Monitor INR
Desipramine	2D6 substrate	No dose adjustments necessary
Ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin	Strong 3A inhibitors	Dose adjust to ivacaftor 150 mg twice weekly
Fluconazole, erythromycin	Moderate 3A inhibitors	Dose adjust to ivacaftor 150 mg once a day
Rifampin, rifabutin, phenobarbital, phenytoin, carbamazepine, St. John's Wort	Strong 3A inducers	Concomitant use not recommended
Oral contraceptives	Not applicable	No dose adjustments necessary
Digoxin, cyclosporine, tacrolimus	P-glycoprotein substrates	Monitor serum concentrations of co- administered medications

CYP, cytochrome P450 isoenzyme; INR, international normalized ratio

tion with CYP3A inhibitors or inducers warrants caution.<sup>1</sup> With strong CYP3A inhibitors such as ketoconazole, ivacaftor's exposure is increased by approximately ninefold, whereas moderate inhibitors of CYP3A increases ivacaftor's exposure by threefold. Conversely, when co-administered with a strong CYP3A inducer, ivacaftor's exposure is decreased by approximately ninefold.<sup>1</sup> Inducers such as St. John's Wort or rifampin are not recommended for use if a patient is currently being treated with ivacaftor.<sup>1</sup> Co-administered medications or ivacaftor may require dose adjustments (Table 1).

Potential inhibition of CYP3A and P-glycoprotein may be seen with ivacaftor and its pharmacologically active metabolite, M1.<sup>1</sup> Increased systemic exposure of medications that are substrates of CYP3A or P-glycoprotein may increase therapeutic effects and likelihood of adverse events. Caution is recommended when substrates such as digoxin are co-administered with ivacaftor.<sup>1</sup>

Several food-drug interactions exist as well. Foods containing 1 or more components that moderately inhibit CYP3A such as Seville oranges or grapefruit should be avoided as they may increase exposure of ivacaftor.<sup>1</sup>

## PHARMACOECONOMIC CONSIDERATIONS

Vertex Pharmaceuticals produced ivacaftor

with \$75 million of assistance in research funding from the Cystic Fibrosis Foundation. The Cystic Fibrosis Foundation shares in the royalties from the sale of ivacaftor in which it intends to reinvest into further CF research.<sup>9</sup>

The annual cost of ivacaftor therapy per patient is approximately \$294,000.<sup>9</sup> Patient assistance programs are available to assist with coverage of costs. Ivacaftor is available at no cost for uninsured patients whose household income is below \$150,000 per year. Deductible and co-pay assistance for commercially insured patients, excluding residents in Massachusetts, pays up to \$88,200 per year in out-of-pocket costs. Independent co-pay assistance foundations exist to provide deductible and co-pay assistance for Medicare and Medicaid patients, and commercially insured patients who need additional help. Once a patient is enrolled, authorization is granted for 1 year.<sup>10</sup>

#### CONCLUSIONS

Since the discovery of the CFTR gene mutation in the late 1980s,<sup>11</sup> there has yet to be a therapeutic agent to act at the cell surface. Therapeutic agents developed prior to ivacaftor targeted the multiorgan dysfunction associated with the CFTR gene mutation. FDA approval of ivacaftor holds promise to the beginning of a new era in CF treatment. It has been proven to improve the activity

Side Effects	<ul> <li>This medication may affect how your liver works.</li> </ul>
	Increases in liver function tests (LFTs) have occurred in patients taking ivacaftor.
	<ul> <li>In patients taking ivacaftor, LFTs will be measured before ivacaftor is started, every 3 months for the first year of therapy, and at least once a year after the first year.</li> </ul>
Drug Interactions	Many medications interact with ivacaftor.
	<ul> <li>Inform your doctor, pharmacist, or other healthcare professionals if you are taking herbal supplements or vitamins.</li> </ul>
	<ul> <li>Inform your doctor, pharmacist, or other healthcare professionals if you have started a new medication or stopped any medications since your last visit.</li> </ul>
	<ul> <li>Dose adjustments may be made if you are taking medications that interact with ivacaftor.</li> <li>Avoid foods containing grapefruit/grapefruit juice or Seville oranges.</li> </ul>
	• It is best if ivacaftor is taken with a fatty meal or snack. Foods like butter, eggs, peanut butter, and cheese pizza are good examples.
	<ul> <li>If pancreatic insufficient, enzymes should be taken with the fatty meal required for ivacaftor administration.</li> </ul>
	<ul> <li>Doses should be separated by 12 hours.</li> </ul>

Table 2 Patient Counceling Take-Home Points

of the CFTR gene, improve lung function, reduce exacerbations, and improve quality of life.<sup>5</sup> It is seemingly well tolerated and offers simplicity in dosing. However, patient and caregiver counseling points are still warranted (Table 2).

Although ivacaftor targets 1 CFTR gene mutation, G551D, it serves as a harbinger for the approval of other therapeutic agents that target at least 1 of the many other remaining CFTR mutations identified. Of these mutations, the most common internationally and in the United States CF population is delta F508. Clinical trials have been planned for patients with CF age 2 to 5 years with gating mutations including G551D. Other trials in progress with extended durations seek to determine the extent of ivacaftor's disease modifying properties. Future research will continue to reveal the importance and relevance of this therapy. This first CFTR potentiator offers a promising future for patients with CF.

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ABBREVIATIONS CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; FDA, Food and Drug Administration; FEV,, forced expiratory volume in 1 second

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