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Overview of Kalydeco® (Ivacaftor) for Treatment of Cystic Fibrosis

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Abstract
Cystic fibrosis (CF) is a genetic disease associated with specific gene mutations that presents with pulmonary inflammation and frequent lung infections, exocrine pancreatic insufficiency, altered sweat composition and declining lung function. Ivacaftor (Kalydeco®) was approved for treatment of cystic fibrosis in patients 6 years of age and older with a G551D mutation on the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Ivacaftor is a CFTR potentiator and does not work in patients with a mutation of the F508del. Efficacy has been demonstrated in several trials with a primary outcome of improved FEV₁, improvements in pulmonary exacerbations, patient-reported decrease in respiratory symptoms and weight gain. Side effects that have been reported include oropharyngeal pain, nasal congestion, abdominal pain, upper respiratory tract infection, rash and dizziness. The drug is metabolized via the CYP3A4 enzyme system and should be monitored for potential drug interactions accordingly. Information on long-term safety is not yet available, but clearly this drug represents an advance in the management of a debilitating disease.

Introduction
On Jan. 31, 2012, Kalydeco® (ivacaftor) received FDA approval for treatment of cystic fibrosis (CF) in patients 6 years of age and older with a G551D mutation on the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Cystic fibrosis is a genetic disease that causes chronic pulmonary inflammation, exocrine pancreatic insufficiency, altered sweat composition and declining lung function. This disease affects approximately 30,000 people in the United States and 70,000 people worldwide. Diagnosis typically occurs early in life, with approximately 70 percent of patients with CF diagnosed before 2 years of age. A variety of CFTR mutations have been identified as causing CF, with different populations having higher prevalence of specific mutations depending on race, ethnicity and geography. The most common mutation is F508del, which is a deletion mutation resulting in improper folding of the CFTR protein leading to little or no CFTR protein on the cell surface. Another mutation, called G551D, is a missense mutation that prevents the binding of adenosine triphosphate (ATP) to the CFTR protein, resulting in an inability to activate the CFTR protein. As of 2012, approximately 87 percent of people with CF were known to have at least one copy of the F508del mutation, and approximately 4 percent of people with CF had at least one copy of the G551D mutation. Because there are numerous genetic mutations that can cause CF, the disease can vary in severity, pathogenesis and treatment approach between individual patients.

Symptoms of CF commonly include pulmonary inflammation, recurrent respiratory infections, airway obstruction, exocrine pancreatic insufficiency and altered sweat composition. Defective CFTR proteins in the respiratory tract lead to reduced chloride transport into the lumen, thereby decreasing surface water content and mucociliary clearance. The heightened mucus retention leads to chronic respiratory infections and inflammation, resulting in lung obstruction and structural damage beginning in infancy, often before symptoms are present. Pancreatic insufficiency is the decreased ability to digest nutrients in the gastrointestinal tract with pancreatic enzymes. This occurs due to obstruction of the pancreatic ducts and autoactivation of trypsin, a digestive enzyme inside the pancreas, resulting in structural damage to the pancreas. Pancreatic insufficiency is present in many phenotypes of CF, with more than 90 percent of diagnosed CF patients beginning to exhibit low pancreatic function before 1 year of age. Individuals affected by CF also typically have a higher concentration of chloride in their sweat compared to individuals without CF.

Screening for CF among newborns is becoming increasingly common; however, diagnosis of CF can be difficult in some patients. Multiple factors can serve as screening tools for CF. A routine newborn screening (NBS) test in infants measures levels of immunoreactive trypsinogen (IRT), a pancreatic protein. A high concentration of IRT constitutes a positive NBS for CF. Family history or presence of CF symptoms can also be screening tools for this disease, as they identify patients who might be at risk for CF. A positive result in any of these screening tests indicates that a patient needs to undergo diagnostic testing.

The current diagnostic standard for CF is a sweat chloride test. This involves collecting sweat from the patient after stimulation of sweating, followed by comparing the resulting chloride concentration to a standard. A chloride concentra-
tion above 60 mmol/L is diagnostic for CF. Concentrations between 40 mmol/L (or 30 mmol/L for patients under 6 months) and 60 mmol/L indicate the need for genotype analysis to assess CFTR gene mutation. A chloride concentration below this range indicates that CF is very unlikely in the patient. When the sweat test results in intermediate values, the presence of two CF-inducing mutations is considered diagnostic for CF. Genotype analysis is available but is not preferred due to inaccuracy and difficult interpretation. Early diagnosis of CF is critical in order to begin treatment as soon as possible to delay progression of the disease.

The aim of many current treatment options is to reduce pulmonary infections, exacerbations, inflammation and deterioration; compensate for pancreatic insufficiency by pancreatic enzyme replacement therapy (PERT); and maintain healthy nutrition and growth. Definitive treatment guidelines that are applicable to all patients with CF are still needed; however, a majority of CF patients utilize a treatment regimen including inhaled antibiotics, hypertonic saline, airway clearance techniques and bronchodilators. Inhaled antibiotics aim to treat respiratory tract infections in CF patients, which are commonly due to Pseudomonas aeruginosa. Multiple antibiotic options are available, including inhaled tobramycin, inhaled aztreonam and azithromycin. Pulmonary exacerbations can be lessened by inhaled hypertonic saline in patients over 6 years of age; however, this may not be effective in patients under 6 years of age. Airway clearance therapy, such as percussion or postural drainage, is recommended for all patients. Inhaled β2-agonists for bronchodilation may be used to reduce exacerbations, but evidence supporting this therapeutic option is not strong. Pancreatic insufficiency should be treated with PERT, even if evidence of malabsorption is lacking. Following CF diagnosis, growth and weight gain in infants should be promoted, as a higher body mass index at 2 years of age is linked to improved lung function in later childhood. Thus, proper nutrition and growth should be lifelong therapeutic goals.

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New treatment options continue to be explored in order to better manage CF disease state.

Pharmacist Information and Counseling Points

Indication: Ivacaftor, a CFTR potentiator, is a U.S. Food and Drug Administration (FDA)-approved treatment option for the management of CF in patients 6 years of age and older. This particular CFTR potentiator is used specifically in patients who are found to have the G551D mutation on the CFTR gene. It should be noted that ivacaftor is not effective in treatment of patients with a homozygous mutation of the F508del mutation. Ivacaftor works to potentiate the nonfunctional CFTR transmembrane protein. By increasing the chance of the CFTR being open, the regular flux of chloride ions in epithelial cells is restored. Due to this normalization of flow, salt and water concentrations will also be stabilized, leading to less viscous mucous secretions and improved respiratory function.

Target Population: Ivacaftor is targeting patients with a G551D mutation of the CFTR protein. Pharmacological treatment options for patients are limited to mucolytics, prophylactic antibiotics, bronchodilators and anti-inflammatory medications. By using ivacaftor, patients may have enhanced therapy by targeting a more direct cause of symptoms instead of only providing symptomatic relief. Pediatric patients are prime targets for CF treatment, and due to the natural progression of the disease, the ability to start therapies in patients at an early age will be beneficial in reducing the degenerative effects and long-term complications of CF. Ivacaftor, being approved for children ages 6 years of age and older, has the potential to be at the forefront of CF pharmacotherapy.

Dosing: Kalydeco® is formulated as a "light blue capsule-shaped, film-coated tablet for oral administration." After clinical studies, the most effective dose was established at 150 mg twice daily. Adult dosing is also recommended for pediatric patients due to similar pharmacokinetics. The adherence to a high-fat diet while using ivacaftor helps to increase medication absorption approximately twofold to fourfold.

Side Effects: Adverse reactions observed in over 10 percent of patients are as follows: oropharyngeal pain, nasal congestion, abdominal pain, upper respiratory tract infection and rash. Some patients have reported feeling dizzy after taking ivacaftor, so it is advised that patients refrain from operating heavy machinery until aware of how they are personally affected by the drug.

Drug Interactions: Because ivacaftor is metabolized via the CYP3A4 enzyme, it is important to be aware of the potential effects of taking other medications which also interact with CYP3A4. A brief guide to drug interactions and dosing adjustments related to changes in medication exposure may be found in the manufacturer’s treatment guide.

Monitoring Parameters: There are several measurements that can be monitored to demonstrate the positive effects of ivacaftor. Such factors include an increase in forced expiratory volume (FEV), decreased respiratory exacerbations, decreased sweat chloride concentration, an increase in body weight and an overall decrease in CF-like symptoms. Increases in alanine aminotransferase (ALT) or aspartate amino transferase (AST) have been observed in ivacaftor patients. Alanine aminotransferase and AST levels should be assessed prior to treatment, then "every three months during the first year of treatment, and annually thereafter." If elevations occur, it is recommended that the patients be monitored monthly if treatment benefit outweighs risk or until numbers return to normal; however, if ALT and/or AST levels are greater than five times the normal upper limit, the drug should be discontinued and therapy should be reevaluated.

Patient Expectations: Patients can expect to see positive results after less than a month of taking ivacaftor. They should notice a decrease in sputum production, easier
breathing patterns and an increase in weight gain.17 Because CF is a chronic disease, their medication regimen will also be chronic, and patients should be made aware that ivacaftor is not a "cure" for CF.

How to Improve Compliance: While chronic medication regimens may seem overwhelming, it is important to stress the benefits of high adherence. In assessing the willingness of pediatric patients to follow their CF therapy, roughly half have been estimated to be noncompliant.20 One benefit to using ivacaftor is the ability to see results in a relatively short period of time after initiation of therapy compared to long-term methods such as airway clearance techniques.21 Seeing quick results will help patients to continue therapy, as "no perceived benefit" has been identified as one of the barriers to effective treatment.22 Furthermore, parental involvement is a highly important aspect in pediatric care. In fact, parents may even be seen as part of the health care team due to their role in facilitating and assisting their child in following CF treatment protocol.22 Therefore, counseling the primary caregiver will be just as important as counseling the pediatric patient. This being said, pharmacists should be able to recognize their own role in this education process. A single case study designed by McClellan, Cohen, and Moffett intending to increase pediatric compliance to CF therapy, attempted the use of a "time out" technique when children resisted compliance.23 Time out may be generalized to the strategy of, "removing the child from reinforcers and reinforcing environments upon noncompliance with demands," and was shown to decrease behavioral conflicts with CF therapy. One given example of time out would be placing a chair in a chair facing the wall for several minutes without permission to talk to others.23 While this method of intervention may seem rudimentary, it demonstrates how reinforcing and encouraging children to adhere to CF therapy can be quite practical.

Cost: As of Nov. 6, 2013, the average wholesale price of 60 (150 mg) tablets (one month’s supply) of ivacaftor is $30,723.60.15 Therefore, the high cost of this medication may be a barrier in effective treatment for some patients.

Literature Review
Several clinical trials have been conducted that support the approval of ivacaftor for the treatment of CF containing the G551D mutation, while also possessing a manageable side effect profile. The first is a phase III clinical trial concluding that the utilization of ivacaftor led to a statistically significant increase in pulmonary function in patients over the age of 12 as defined by forced expiratory volume in one second (FEV1).4 The next study is a phase III clinical trial concluding a similar increase in pulmonary function as defined by FEV1 in pediatric subjects between the ages of 6 and 11.5 The third study is a phase II clinical trial assessing the safety and function of ivacaftor in CF that is homozygous for the F508del mutation concluding that ivacaftor, while reasonably safe, is not effective in this subpopulation.6 The final study is a phase II clinical trial that provides a look into the safety profile of ivacaftor in patients with CF containing the G551D mutation, and suggests that the drug is safe for this subpopulation.24 These four clinical trials are key to understanding the therapeutic benefit of ivacaftor in patients with CF containing the G551D mutation.

Ramsey et al. conducted the main efficacy trial supporting the use of ivacaftor for improved lung function in patients with CF containing the G551D mutation. The study was a 48-week, phase III clinical trial. Eligible patients for this trial included those aged 12 years or older who had a previous diagnosis of CF, possessed the G551D mutation on at least one CFTR allele, and had an FEV1 between 40 and 90 percent of the predicted value given age, sex and height. No specific exclusion criteria were provided. The primary endpoint for the trial was the absolute change in FEV1 from baseline at week 24. Secondary endpoints included change in FEV1 from baseline at week 48, the time to pulmonary exacerbation, patient reported respiratory symptoms, weight change and CFTR function (via sweat chloride test).4 In the study, 161 patients were randomly assigned to one of two treatment groups: ivacaftor 150 mg twice daily (n=83) or placebo (n=78). The randomization was stratified for both age (<18 years or ≥18 years) and baseline pulmonary function (<70 percent or ≥70 percent predicted FEV1 level). The stratification process was successful; lending equally distributed demographics across the two treatment groups. Power calculations had concluded that 160 patients would provide 80 percent power to detect a change of 4.5 percent in the predicted FEV1. All patients received their medications twice daily for a full 48 weeks and were allowed to remain on all other medications with an FDA-approved indication for CF, such as dornase alfa and inhaled antibiotics. Primary outcome was assessed for all patients at week 24 and secondary outcomes were assessed for all patients at day 15, week 24, and week 48.4 At week 24, patients in the ivacaftor group witnessed a 10.4 percent increase in FEV1 compared to a 0.2 percent decrease in the placebo group (p<0.001). The effect on FEV1 was noted to be statistically significant at day 15, and was retained throughout all 48 weeks of treatment. This change in FEV1 was analyzed over subgroups defined by baseline FEV1, age and sex; there was no apparent difference in the efficacy of ivacaftor with respect to change in FEV1 across any of these different subgroups. In addition to change in baseline FEV1, other outcomes such as pulmonary exacerbations (p=0.001), patient reported respiratory symptoms (p<0.001), weight gain (p<0.001) and CFTR function (p<0.001) were all improved in the ivacaftor treatment group.4 Overall, patients in the placebo group experienced more adverse events than patients in the ivacaftor group, likely due to the decreased level of pulmonary exacerbation in patients treated with ivacaftor. Forty-two percent of subjects in the placebo group experienced a serious adverse event while only 24 percent of subjects in the ivacaftor group experienced such an event. However, two patients in the ivacaftor group experienced hypoglycemia while no patients in the placebo group experienced this adverse event. The study...
yielded no adverse events that were concluded to have arisen as a result of ivacaftor treatment. All patients who were initiated on either of the treatment drugs completed the trial with the exception of one subject, a member of the placebo group who dropped out of the study following a severe pulmonary exacerbation. Ultimately, ivacaftor was not associated with any significant adverse events not seen in the placebo group.\textsuperscript{4}

Limitations of this trial include restrictive inclusion criteria and limited documentation on use of other CF medications. The inclusion criteria only allowed patients who were between 40 and 90 percent of predicted FEV\textsubscript{1} levels.\textsuperscript{4} This prevents the most critical of patients from enrolling in the study, limiting the external validity of the trial. It must also be noted that the trial utilized ivacaftor only as add-on therapy to an established CF treatment regimen. The protocol did require that patients be on their current medication regimen for a full year prior to trial initiation, but it is unclear what effect the impact that those drugs may or may not have on the efficacy value of ivacaftor.\textsuperscript{4}

The second main efficacy trial, by Davies et al., is a 48-week phase III study conducted in children aged 6 to 11. Eligible patients for this trial included children aged 6 to 11 with a confirmed diagnosis of CF containing the G551D mutation. Additionally, subjects were required to have a predicted FEV\textsubscript{1} between 40 and 105 percent given their age, sex and height. The primary endpoint for the study was absolute change in FEV\textsubscript{1} from baseline at week 24. Secondary endpoints included change in FEV\textsubscript{1} from baseline at week 48, weight change, CFTR function (via sweat chloride tests), patient and parent reported respiratory symptoms, and safety.\textsuperscript{5}

In the study, 52 patients were randomly assigned to one of two treatment arms: placebo (n=26) or ivacaftor 150 mg twice daily (n=26). There was no randomization stratification or power calculation. All patients received their treatment medication twice daily for a full 48 weeks and were allowed to remain on all medications that possessed an FDA-approved indication for CF. Endpoints were assessed at follow-up meetings every eight weeks (weeks 8, 16, 24, 32, 40, and 48) in addition to day 15.\textsuperscript{5}

With regard to change in baseline FEV\textsubscript{1} at week 24, the ivacaftor group witnessed an increase of 12.6 percent compared to an increase of 0.1 percent in the placebo group (p=0.001). This statistically significant effect was noted at day 15 and was maintained throughout the course of the clinical trial to the week-48 endpoint. Other secondary outcomes that showed improvement in the ivacaftor treatment group compared to the placebo group included weight gain (p=0.001), patient and parent reported respiratory symptoms (p=0.109; p=0.033) and CFTR function (p<0.001).\textsuperscript{5}

The total incidence of adverse events was similar between the two treatment groups. The ivacaftor group experienced the following side effects more often than the placebo group: oropharyngeal pain, headache, nasopharyngitis, upper respiratory tract infection, otitis media, diarrhea and increased blood eosinophil count. Serious adverse events such as pulmonary exacerbation and productive cough were witnessed infrequently with no difference between treatment groups. These results mimic those seen in the adult clinical trials and suggest that ivacaftor is well-tolerated in the pediatric population aged 6 and above.\textsuperscript{5}

The main limitation of this trial is a clear lack of power. This inadequacy is quite common in pediatric clinical trials due to a multitude of factors including, but not limited to, the low incidence of CF and parental concern over experimental treatments. Even so, the lack of power must be considered when trying to determine the external validity of the trial.

The third efficacy trial, conducted by Flume et al., is a 16-week (followed by a 96-week open-label extension period) phase II study. Eligible patients for this trial included clinically stable subjects over the age of 12 who had been diagnosed with CF containing two F508del alleles (homozygous). Additionally, subjects were required to have a predicted FEV\textsubscript{1} above 40 percent given their age, sex and height. Subjects remained on their pre-study medication regimens throughout the study with the exception of hypertonic saline and known inducers/inhibitors of CYP3A4. The primary endpoints for the study were (1) absolute change in FEV\textsubscript{1} from baseline at week 16 and (2) safety as evaluated by adverse events, lab values, vital signs and physical examinations.\textsuperscript{6}

In the study, 140 patients were randomly assigned in a 1:4 ratio to one of two treatment arms: placebo (n=28) or ivacaftor 150 mg twice daily (n=112). There was no randomization stratification or formal power calculation. All patients received their treatment medication twice daily for a full 48 weeks and were allowed to remain on all medications that possessed an FDA-approved indication for CF. Endpoints were assessed at follow-up meetings every eight weeks (8, 16) in addition to day 15. Any patient who experienced a greater than 10 percent increase in FEV\textsubscript{1} at any time point during the 16-week treatment period qualified to enroll in the 96-week open-label extension.\textsuperscript{6}

With regard to change in baseline FEV\textsubscript{1} at week 16, the ivacaftor group witnessed an increase of 1.7 percent compared to placebo, which was not statistically significant (p=0.15). Twenty-eight members of the ivacaftor group (25%) and six members of the placebo group (21.4%) qualified for the open-label extension period as a result of their increased FEV\textsubscript{1}. The difference in FEV\textsubscript{1} was not statistically significant in these patients at the conclusion of the open-label extension (p=0.46).\textsuperscript{6}

The overall safety profile was similar in both treatment arms. However; cough, nausea, rash and contact dermatitis occurred more often in the ivacaftor group; none of these events was considered severe. On the other hand, pulmonary exacerbation occurred more often in the placebo group. Few members of the ivacaftor group experienced life-threatening events including fatigue, depression and suicidal ideation (n=1; 0.9%) as well as severe events including nasal congestion, epistaxis, diarrhea, rash, headache, and arthritis (n=10; 9.1%).
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8.9%). Three subjects (2.7%) in the ivacaftor group discontinued the study drug due to adverse events.6

This study allows for the conclusion that ivacaftor is not effective in patients homozygous for the F508del mutation. The study does, however, provide additional information regarding the safety of ivacaftor in patients with diagnosed CF. The adverse event profile witnessed in this study supports the conclusion that ivacaftor is well-tolerated in patients over the age of 12 diagnosed with CF.

The final trial, conducted by Accurso et al., is a phase II study designed to assess the safety and adverse event profile of ivacaftor in patients who have CF containing the G551D mutation. Eligible patients for this trial included those over the age of 18 who had been diagnosed with CF and possessed a G551D mutation on at least one CFTR allele; patients also had to have an FEV1 of 40 percent or more of the estimated level for age, sex and height. No specific exclusion criteria were reported. The primary endpoint for the study was to assess the safety and adverse event profile of ivacaftor. Secondary endpoints included markers of CFTR function (nasal potential difference and sweat chloride concentration), pulmonary performance (FEV1) and quality of life (Cystic Fibrosis Questionnaire-revised; CFQ-R).24

This trial was designed as a two-part study. In part one, 20 subjects were placed into one of five treatment groups: placebo (n=4), ivacaftor 25/75 mg (n=4), ivacaftor 75/25 mg (n=4), ivacaftor 75/150 mg (n=4), and ivacaftor 150/75 mg (n=4), where the first strength indicates the dose received prior to a 14-day washout period and the second strength indicates the dose received after the washout period. Subjects were given their initial treatment dose twice daily for 14 days; a 14-day washout period followed; subjects were then given their second treatment dose twice daily for an additional 14 days. Primary and secondary endpoints were assessed for all patients at the end of each 14-day treatment period. In part two, 19 subjects (different from the participants in part one) were placed into one of three treatment groups: placebo (n=4), ivacaftor 150 mg (n=8), ivacaftor 250 mg (n=7). Subjects were given their treatment doses twice daily for a continuous 28 days after which primary and secondary endpoints were assessed.24

The primary outcome for both part one and part two of this clinical trial yielded relatively few side effects associated with the use of ivacaftor at any dosage strength. There were 22 reported instances of drug-associated moderate or severe adverse events. Some of the more prominent adverse events that were reported included elevated blood glucose, body aches, glycosuria and nausea. Secondary efficacy outcomes yielded no statistical significance over placebo.24 However, the low enrollment of the study combined with a lack of power make the lack of statistical efficacy over placebo moot point.

These four trials outline the safety and efficacy data that is currently available for the use of ivacaftor in humans. However, it must also be noted that all four of these clinical trials were both funded and designed by the manufacturer of ivacaftor, Vertex Pharmaceuticals™, but given the infancy of the compound, orphan nature of the drug in question and the fact that these were the clinical trials involved in the FDA approval process for the medication; this manufacturer-driven study process is an economic necessity. Furthermore, the transparency with which the authors addressed their potential conflicts of interest limits any potential concern for bias. An additional point to consider is that given the genetic nature of CF, pulmonary function can begin to decrease well before age 6, meaning that these undeveloped patients are in a prime position to alter the course of their disease. It would be beneficial to see a clinical trial in patients younger than age 6, in order to determine if ivacaftor can maintain its thus-far impressive clinical impact on a younger set of patients. Currently, Vertex Pharmaceuticals™ is recruiting for a phase III clinical trial to assess the safety and efficacy of ivacaftor in patients aged 2 to 5.25

Ultimately, while the G551D mutation impacts less than 10 percent of all patients with a CF diagnosis, the success for ivacaftor with regard to improvement of clinical indicators in this subpopulation is a definitive step forward. In particular, consistent double-digit improvement of FEV1 suggests a significant boost in lung function when compared to other commonly used CF therapies.4 Unfortunately, it remains to be seen what long-term impact ivacaftor may have on life-expectancy and long-term quality of life in patients with CF.

Conclusion
Kalydeco® (ivacaftor) has been approved for the treatment and management of CF in pediatric patients as of Jan. 31, 2012. This medication is approved for patients 6 years of age and older, who have a G551D mutation on the CFTR gene.14,15 Ivacaftor's novelty comes from its genetic specificity for the aforementioned CF mutation.14,15 Because a majority of CF patients are diagnosed before they reach the age of 2, it is important to have medication therapy protocols approved and at the ready for children.3 Short-term effects have shown promise with increasing FEV1 values; however, information on long-term use is uncertain. Overall, introduction of ivacaftor into medication regimens is a positive step for the treatment of pediatric patients living with cystic fibrosis.

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