New Drug Review

Generic Name: (ivacaftor)
Trade Name: (Kalydeco®)
Manufacturer: Vertex Pharmaceuticals
Food and Drug Administration Approval Date: January 31, 2012
Product Launch Date: April 18, 2012

Overview/Summary

Cystic fibrosis is a rare autosomal recessive disease characterized by abnormalities in chloride and sodium transportation at cellular levels due to mutations in the cystic fibrosis transmembrane regulator (CFTR) gene.[1] The disease affects multiple organs including the pancreas, sweat glands, intestines, liver, and reproductive tract; however, it's effect on the respiratory system is the most common cause of morbidity and mortality.[2] CFTR is a protein which normally acts like an ion channel for chloride transmembrane transportation; therefore, defective protein leads to a reduction of CFTR-related chloride secretion which is associated with a secondary increase in epithelial sodium channel-mediated Na+ caused by the absence of the inhibitory activity of the normal CFTR. Defective CFTR protein leads to the production of abnormally viscid mucus which impacts the airways, obstructing them, and altering the normal mechanisms of mucociliary clearance. Patients with cystic fibrosis tend to develop respiratory tract infections, including those colonized with *Pseudomonas aeruginosa*, and persistent lung inflammation which leads to a loss of normal lung function and respiratory failure.[1]

Several CFTR mutations have been identified, the most common being class II type mutations consisting of the deletion of three nucleotides resulting in the loss of phenylalanine at the 508 position on the protein (F508). G551D is a class III mutation which is detected in five to ten percent of cystic fibrosis patients and yields an abnormal protein which is able to translocate to the cell surface, but which has impaired gating/opening function. Therapies aimed at targeting various mutations that lead to malfunctioning of CFTR protein have become increasingly popular; however, because of the specificity of such therapies, broader therapeutic approaches, including those focused on the treatment of respiratory tract infection and reduction of mucus thickness should also be utilized in cystic fibrosis patients.[1]

Kalydeco® (ivacaftor) is a cystic fibrosis transmembrane conductance regulator potentiator Food and Drug Administration (FDA)-approved for the treatment of cystic fibrosis in patients at least six years of age who have a G551D mutation at the CFTR gene. If the patient's genotype is unknown, an FDA-cleared cystic fibrosis mutation test should be used to detect the presence of the G551D mutation. Ivacaftor is not effective in patients with cystic fibrosis who are homozygous for the Delta F508 mutation in the CFTR gene, and the agent has not been evaluated in other populations with cystic fibrosis. As a potentiator of the CFTR protein, ivacaftor facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the G551D-CFTR protein.[3] In two placebo-controlled trials, treatment with ivacaftor increased forced expiratory volume in one second after 24 weeks, and the treatment effect was maintained throughout 48 weeks.[3,4] Clinical guidelines currently do not address the role of ivacaftor for the management of cystic fibrosis. Of note, ivacaftor is currently being evaluated in patients with homozygous Delta F508 mutation.

Pharmacokinetics

Table 1. Pharmacokinetics[5]

Generic Name	Bioavailability* (%)	Renal Excretion (%)	Metabolism	Active Metabolites	Serum Half-Life (hours)
Ivacaftor	Not reported	Negligible (% not reported)	CYP3A	M1	12

*Ninety-nine percent bound to plasma proteins

Clinical Trials

In a trial by Ramsey et al, one hundred and sixty one patients ≥12 years of age with cystic fibrosis were randomized to receive ivacaftor 150 mg twice-daily or placebo for 48 weeks. All patients continued pre-trial medications, with the exception of hypertonic saline. After 24 weeks, ivacaftor significantly increased forced expiratory volume in one second (FEV_1) compared to placebo (10.4 vs 0.2 percentage points; *P*<0.001), and the significant treatment effect was maintained throughout the 48 weeks (*P*<0.001). Patients receiving ivacaftor reported significant reductions in respiratory symptoms (treatment difference, 8.6 points; *P*<0.001) and achieved significant weight gain compared to those receiving placebo (3.1 vs 0.4 kg; *P*<0.001). After 15 days of treatment, sweat chloride concentrations began to decrease in patients receiving ivacaftor, a treatment effect that was significant after 24 (treatment effect, -47.9 mmol/L; *P*<0.001) and 48 weeks (treatment effect, -48.1; *P*<0.001). Significantly more patients who received ivacaftor were free from pulmonary exacerbations at 48 weeks (67 vs 41%; hazard ratio, 0.455; *P*=0.001), and there were fewer exacerbations in patients receiving ivacaftor which led to hospitalization (21 vs 31). Adverse events reported more frequently with ivacaftor were headache, upper respiratory tract infection, nasal congestion, rash, and dizziness. The incidences of pulmonary exacerbation, cough, hemoptysis, and decreased pulmonary function were higher with placebo.[4]

According to the package labeling for ivacaftor, in a second placebo-controlled trial of cystic fibrosis patients six to eleven years of age (N=52) treatment with ivacaftor resulted in significant improvements in FEV_1 after 24 weeks (*P*<0.0001), that were maintained throughout the 48 week long trial. In this trial, there was no difference in patient reported improvements in respiratory symptoms between the two treatments; however, patients receiving ivacaftor gained more weight compared to those receiving placebo (week 24; treatment difference, 1.9 kg; *P*=0.0004 and week 48; treatment difference, 2.8 kg; *P*=0.0002).[3]

Table 2. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results	Study Grade*
Ramsey et al[4] Ivacaftor 150 mg BID vs placebo All patients continued to take their pre-trial medications with exception of hypertonic saline.	DB, PC, RCT Patients ≥12 years of age with cystic fibrosis, G551D mutation on ≥1 CFTR allele, and FEV_1 40 to 90%	N=161 48 weeks	Primary: Absolute change from baseline through week 24 in the percent of predicted FEV_1 Secondary: Change from baseline through week 48 in the percent of predicted FEV_1, patient-reported respiratory symptoms through week 24 and week 48, change in baseline weight, change in baseline concentration of sweat chloride, number and duration of pulmonary exacerbations, total number of days of hospitalization for pulmonary exacerbations, safety	Primary: Through week 24, ivacaftor significantly increased predicted FEV_1 compared to placebo (10.4 vs -0.2 percentage points; *P*<0.001). The improvement with ivacaftor reflected a mean increase in FEV_1 of 0.367 L compared to a mean increase in FEV_1 of 0.006 L with placebo (treatment effect, 0.361 L; *P*<0.001) throughout week 24, which corresponded to a relative change from baseline of 17.2 and 0.1% with ivacaftor and placebo. An effect with ivacaftor was noted on day 15 of treatment (treatment effect, 9.3 percentage points; *P*<0.001). Secondary: A significant treatment effect was maintained throughout the trial, with a change in the percent of predicted FEV_1 from baseline through week 48 that was 10.5 percentage points greater with ivacaftor compared to placebo (*P*<0.001). Patients receiving ivacaftor had an improvement in scores on the CFQ-R respiratory domain (indicated a reduction in respiratory symptoms) compared to placebo. At 48 weeks, the scores increased by 5.9 points with ivacaftor and decreased by 2.7 points with placebo (treatment effect, 8.6 points; *P*<0.001). By week 48, weight gain was higher with ivacaftor compared to placebo (3.1 vs 0.4 kg; treatment effect, 2.7 kg; *P*<0.001). Through week 24, the change from baseline in sweat chloride was greater with ivacaftor compared to placebo (-48.7 vs -0.8 mmol/L; treatment effect, -47.9 mmol/L; *P*<0.001). The values for sweat chloride were 47.8 and 100.0 mmol/L with ivacaftor and placebo at week 24. A treatment effect was initially observed at day 15 and was maintained through week 48 (treatment effect, -48.1; *P*<0.001). At week 48, a total of 67 and 41% of patients receiving ivacaftor and placebo were free from pulmonary exacerbations (HR, 0.455;	Good

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results	Study Grade*
				P=0.001), corresponding to a 55% reduction in the risk of pulmonary exacerbation with ivacaftor. There were 47 and 99 exacerbations in patients receiving ivacaftor and placebo. A total of 21 and 31 pulmonary exacerbations with ivacaftor and placebo led to hospitalization. The number of days of hospitalization for pulmonary exacerbations per patient (normalized to a 48-week period) was shorter with ivacaftor (3.9±13.6 vs 4.2±8.7; *P*=0.03). The incidence of adverse events was similar between the two treatments. Ivacaftor was associated with a higher incidence of adverse events leading to interruption of study medication (13% vs 6%). All patients who interrupted treatment were able to resume taking the study drug and complete the trial, with exception of one patient receiving placebo (due to severe respiratory distress). One patient receiving ivacaftor discontinued treatment due to increased hepatic enzyme levels. Pulmonary exacerbation, cough, hemoptysis, and decreased pulmonary function occurred less frequently with ivacaftor compared to placebo. Adverse events that occurred more frequently with ivacaftor were headache, upper respiratory tract infection, nasal congestion, rash, and dizziness. A total of 53 serious adverse events were reported, and these events occurred less frequently with ivacaftor (24% vs 42%).	

*Study grading according to Agency for Healthcare Research and Quality (AHRQ) (See Appendix I for definition of ratings). Studies falling outside of the grading criteria defined by AHRQ will be noted as "Not Applicable". This indicates that the grading criteria did not appropriately fit the design of the included study, but that it was included due to the potential value of the presented data.
Drug regimen abbreviations: BID=twice-daily
Study abbreviations: DB=double-blind, HR=hazard ratio, PC=placebo-controlled, RCT=randomized controlled trial
Miscellaneous abbreviations: CFQ-R=Cystic Fibrosis Questionnaire-revised, CFTR=cystic fibrosis transmembrane conductance regulator, FEV_1=forced expiratory volume in one second

Special Populations

Table 3. Special Populations[3]

Population	Precaution
Elderly	Clinical trials did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger patients.
Renal Dysfunction	Not studied in renal dysfunction. However, caution is recommended in patients with severe renal impairment (CrCL≤ 30 mL/min) or end stage renal disease
Hepatic Dysfunction	No dosage adjustment required with mild hepatic impairment. Hepatic dosage adjustment required with moderate impairment (Child-Pugh Class B; a dose of 150 mg once-daily is recommended. Not studied with severe hepatic impairment (Child-Pugh Class C). However, the dose of ivacaftor should generally not exceed 150 mg daily in patients with severe hepatic impairment.
Pregnancy/ Nursing	Pregnancy category: B. Excretion through breast milk: Unknown; use with caution.
Children	Safety and efficacy in children <6 years of age have not been established.
Other	Dosage adjustment required with co-administration of CYP3A inhibitors; a dose of 150 mg twice weekly is recommended with strong CYP3A inhibitors and a dose of 150 mg once-daily is recommended with moderate CYP3A4 inhibitors.

CrCL = creatinine clearance

Adverse Drug Events

Table 4. Adverse Events Reported Frequency (%)[3]

Adverse Event	Kalydeco® (Ivacaftor); n=109	Placebo; n=104
Abdominal pain	16	13
Acne	4 to 7	-
Arthralgia	4 to 7	-
Aspartate aminotransferase increased	4 to 7	-
Bacteria in sputum	4 to 7	-
Blood glucose increased	4 to 7	-
Diarrhea	13	10
Dizziness	9	1
Headache	24	16
Hepatic enzyme increased	4 to 7	-
Musculoskeletal chest pain	4 to 7	-
Myalgia	4 to 7	-
Nasal congestion	20	15
Nasopharyngitis	15	12
Nausea	12	11
Oropharyngeal pain	22	18
Pharyngeal erythema	4 to 7	-
Pleuritic pain	4 to 7	-
Rash	13	7
Rhinitis	4 to 7	-
Sinus congestion	4 to 7	-
Sinus headache	4 to 7	-
Upper respiratory tract infection	22	14
Wheezing	4 to 7	-

-Event not reported.

Contraindications/Precautions

There are no documented contraindications with ivacaftor.[3]

Alanine and aspartate transaminases should be assessed prior to initiating ivacaftor, every three months during the first year of treatment, and annually thereafter. If elevated levels are observed the patient should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients with alanine or aspartate transaminase levels greater than five times the upper limit of normal. Following resolution of transaminase elevations, consider the benefits and risks of resuming treatment.[3]

Drug Interactions

- Use of ivacaftor with strong cytochrome P450 3A4 inducers is not recommended.[3]
- The dose of ivacaftor should be reduced to 150 mg twice-a-week with concomitant administration of strong CYP3A inhibitors.[3]
- Use of ivacaftor with food containing grapefruit or Seville oranges should be avoided.[3]

Dosage and Administration

Table 5. Dosing and Administration[3]

Adult Dose	Pediatric Dose	Availability
Treatment of cystic fibrosis in patients at least six years of age who have a G551D mutation at the cystic fibrosis transmembrane conductance regulator gene: Tablet: 150 mg BID*	Safety and efficacy in children <6 have not been established.	Tablet: 150 mg

BID=twice-daily
*The dose should be administered with fat-containing food.

Potential Advantages

- Kalydeco® (ivacaftor) is another option in the management of cystic fibrosis.
- Kalydeco® (ivacaftor) is the first available treatment that targets the defective cystic fibrosis transmembrane regulator protein, which is the underlying cause of cystic fibrosis.
- Compared to placebo, treatment with Kalydeco® (ivacaftor) resulted in significant improvements in lung function, decreases in respiratory symptoms and pulmonary exacerbations, decreases in sweat chloride concentrations, and increases in weight in patients with cystic fibrosis.

Potential Disadvantages/Unanswered Questions

- Mutation specific therapies, including Kalydeco® (ivacaftor), may not work in all cystic fibrosis patients.
- No long term data with Kalydeco® (ivacaftor) is available.
- No data on a potential mortality benefit of Kalydeco® (ivacaftor) is available.

Clinical Guidelines

Table 6. Clinical Guidelines

Clinical Guideline	Recommendations
Cystic Fibrosis Foundation: **Cystic Fibrosis Pulmonary Recommendations: Chronic Medications for Maintenance of Lung Health (2007)**[6]	Aerosolized antibiotics • For patients with cystic fibrosis, six years of age and older, who have moderate to severe lung disease with *Pseudomonas aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled tobramycin to improve lung function and reduce exacerbations is strongly recommended. • For patients with cystic fibrosis, six years of age or older, who are asymptomatic or with mild lung disease, and with *P aeruginosa* persistently present in cultures of the airways, chronic use of inhaled tobramycin to reduce exacerbations is recommended. • For patients with cystic fibrosis, six years of age or older, with *P*

Clinical Guideline	Recommendations
	aeruginosa persistently present in cultures of the airways, there is insufficient evidence to recommend for or against routinely providing other chronically inhaled antibiotics (i.e., colistin, gentamicin, ceftazidime) to improve lung function and reduce exacerbations. Recombinant Human DNase • For patients with cystic fibrosis, six years of age or older, with moderate to severe lung disease, chronic use of dornase alfa to improve lung function and reduce exacerbations is strongly recommended. • For patients with cystic fibrosis, six years of age or older, and asymptomatic or with mild lung disease, chronic use of dornase alfa to improve lung function and reduce exacerbations is recommended. Hypertonic saline • For patients with cystic fibrosis, six years of age or older, chronic use of inhaled hypertonic saline to improve lung function and to reduce exacerbations is recommended. Anti-inflammatory agents • For patients with cystic fibrosis, six years of age or older, and without asthma or allergic bronchopulmonary Aspergillosis, the routine use of inhaled corticosteroids to improve function and to reduce exacerbations is not recommended. • For patients with cystic fibrosis, between six to 18 years of age, and without asthma or allergic bronchopulmonary Aspergillosis, chronic use of oral corticosteroids to improve lung function and to reduce exacerbations is not recommended. • For adult patients with cystic fibrosis without asthma or allergic bronchopulmonary Aspergillosis, there is insufficient evidence to recommend for or against the chronic use of oral corticosteroids to improve lung function and to reduce exacerbations. • For patients with cystic fibrosis, six years of age or older, and with forced expiratory volume in one second greater than 60% predicted, chronic use of oral ibuprofen to slow the loss of lung function is recommended. • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing the chronic use of leukotriene modifiers to improve lung function and to reduce exacerbations. • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing the chronic use of cromolyn to improve lung function and to reduce exacerbations. Macrolide antibiotics • For patients with cystic fibrosis, six years of age or older, and with *P aeruginosa* persistently present in cultures of the airways, chronic use of azithromycin to improve lung function and to reduce exacerbations is recommended.

Clinical Guideline	Recommendations
	Antistaphylococcal antibiotics • For patients with cystic fibrosis, prophylactic use of oral antistaphylococcal antibiotics to improve lung function to reduce exacerbations is not recommended. Bronchodilators • For patients with cystic fibrosis, six years of age or older, chronic use of inhaled β2-adrenergic receptor agonists to improve lung function is recommended. • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing the chronic use of inhaled anticholinergic bronchodilators to improve lung function. • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing chronic use of inhaled or N-acetylcysteine to improve lung function and to reduce exacerbations.

Conclusions

Kalydeco® (ivacaftor) is the first cystic fibrosis transmembrane conductance regulator potentiator Food and Drug Administration (FDA)-approved for the treatment of cystic fibrosis in patients at least six years of age who have a G551D mutation at the cystic fibrosis transmembrane regulator (CFTR) gene. Ivacaftor facilitates increased chloride transport via potentiation of the channel-open probability (or gating) of the G551D-CFTR protein.[3] G551D is a class III CFTR mutation which yields an abnormal protein able to translocate to the cell surface that has impaired gating/opening function. Defective CFTR protein in patients with cystic fibrosis leads to the production of abnormally viscid mucus which impacts the airways through obstruction and alters the normal mechanisms of mucociliary clearance.[1] If the patient's genotype is unknown, a FDA-cleared cystic fibrosis mutation test should be used to detect the presence of the G551D mutation. Ivacaftor is not effective in patients with cystic fibrosis who are homozygous for the Delta F508 mutation of the CFTR gene, and the agent has not been evaluated in other populations of patients with cystic fibrosis.[3]

In two placebo-controlled trials, treatment with ivacaftor increased forced expiratory volume in one second after 24 weeks, and the treatment effect was maintained throughout 48 weeks. In addition, treatment with ivacaftor was associated with improvements in respiratory symptoms and decreases in sweat chloride concentrations and pulmonary exacerbations in one trial. In both trials, patients receiving ivacaftor gained more weight compared to placebo.[3,4] There is currently a lack of long term data with ivacaftor, and its benefits on mortality, if any, are unclear at this time. Current clinical guidelines do not provide any guidance as to the role of ivacaftor in the management of cystic fibrosis. The G551D mutation is detected in five to ten percent of cystic fibrosis patients. Because of the specificity of such a therapy, broader therapeutic approaches, including those focused on the treatment of respiratory tract infection and reduction of mucus thickness should also be utilized in cystic fibrosis patients.[1] Of note, ivacaftor is currently being evaluated in patients with homozygous Delta F508 mutation.

Appendix IV: Agency of Healthcare Research and Quality (AHRQ) Study Grading Definitions for Randomized Controlled Trials

Source: *U.S. Preventive Services Task Force Procedure Manual*. AHRQ Publication No. 08-05118-EF, July 2008 Agency for Healthcare Research and Quality, Rockville, MD. http://www.ahrq.gov/clinic/uspstf08/methods/procmanualap7.htm.

Randomized Controlled Trials		
Definition of Ratings from Above Criteria	**Good**	Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. Intention to treat analysis is used.
	Fair	Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done.
	Poor	Studies will be graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention to treat analysis is lacking.

References

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2012 Q1 and Q2 Kalydeco Utilization

YearMonth Submitted	Drug Label Name	Claim Count	Sbm Qty Dispense	Sbm Days Supply	App Dispensing	App Total Amount
201201	Kalydeco 150mg Tab	0	0	0	0	0
201202	Kalydeco 150mg Tab	0	0	0	0	0
201203	Kalydeco 150mg Tab	0	0	0	0	0
201204	Kalydeco 150mg Tab	0	0	0	0	0
201205	Kalydeco 150mg Tab	0	0	0	0	0
201206	Kalydeco 150mg Tab	0	0	0	0	0

DIVISION OF HEALTH CARE FINANCING AND POLICY
NEVADA MEDICAID
DRUG USE REVIEW (DUR) BOARD
PROPOSED PRIOR AUTHORIZATION CRITERIA

Kalydeco® (ivacaftor) is a covered benefit of Nevada Medicaid for recipients who meet the criteria for coverage.

1. Coverage and Limitations:
Authorization will be given if the following criteria are met and documented:

a. The recipient has a diagnosis of cystic fibrosis.
AND
b. There is documentation that the recipient has had an FDA-approved cystic fibrosis mutation test confirming presence of the G551D gene mutation.

2. PA Guidelines:
Prior Authorization approval will be for 1 year.

3. Quantity Limits:
60 tablets per rolling 25 days