Drug Use Research & Management Program
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Month/Year of Review: June 2012
Generic Name: Ivacaftor
Comparator Therapies: None

End date of literature search: April 2012
Brand Name (Manufacturer): Kalydeco (Vertex Pharmaceuticals)
Dossier received: Yes

FDA Approved Indications: Ivacaftor is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator used for the treatment of cystic fibrosis (CF) in patients 6 years and older who have the G551D mutation in the CFTR gene (approximately 4% of CF patients). If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the G551D mutation.[1] Ivacaftor is given twice daily as a 150 mg capsule with fatty food to increase absorption.

Key Questions:

1. Is ivacaftor more effective than currently available preferred agents for the treatment of CF?
2. Is ivacaftor better tolerated than currently available preferred agents?
3. Are there specific populations which ivacaftor would be better tolerated or more effective?

Conclusions: There is moderate level of evidence to suggest that ivacaftor is superior to placebo in patients (≥12 years old) with theG551D mutation, as illustrated by an increase in FEV_1. There is also moderate evidence that ivacaftor is well tolerated with adverse effects resulting in discontinuations rates less than placebo. There are no head-to-head trials comparing ivacaftor to other CF treatments. Changes in FEV_1 with ivacaftor were similar to therapies used in the chronic management of CF. There is insufficient evidence to grade ivacaftor treatment in children under 12. Limited unpublished data suggests similar efficacy and safety as in patients over 12 years of age. Due to the robust nature of the results and benefits that outweigh the risks, use in this population is also recommended.

The efficacy and safety evaluation of ivacaftor is limited by small study populations; study durations of only one year and unpublished data. Ivacaftor has been shown to be effective only in the CF population with the G551D mutation, making ivacaftor a treatment option in only a small percentage of patients with CF. The effects of ivacaftor on long term disease progression are unknown.

Recommendations:

It is recommended to use clinical prior authorization criteria (Appendix) to limit the use of ivacaftor to patients that are six years and older, diagnosed with CF, have the G551D mutation in the CFTR gene, is prescribed by or in consultation with a pulmonologist or a practitioner at an accredited Cystic Fibrosis Center, and has had an adequate trial of standard medication therapy. Renewal criteria will be implemented to monitor for a clinical response and adherence.

Summary:

CF is a genetic disease which can affect multiple organs, in which lung disease is responsible for approximately 85% of the mortality. The effects on the lungs are characterized by dehydration of the airway surface liquid and impaired mucociliary clearance which leads to chronic pulmonary infection.[2] Current available treatments for CF focus on symptom management. Guidelines for chronic treatment of CF suggest that there is good evidence that inhaled tobramycin and dornase alfa provide substantial benefit to patients with moderate to severe lung disease. Studies have shown improvement in FEV_1 ranging from 7.8%-12% with inhaled tobramycin and 5.8%-7.3% with dornase alfa. There is also fair evidence to suggest that macrolide antibiotics provide substantial benefit for all levels of disease with improvements in FEV_1 from 3.6%-6.2%.[2] Hypertonic saline, oral nonsteroidal anti-inflammatory drugs (NSAIDS) and inhaled $beta_2$ agonists also play a role in the chronic management of CF.[2]

Efficacy:

The primary morbidity associated with CF is loss of pulmonary function. An important outcome in monitoring pulmonary function is the absolute change in forced expiratory volume in one second (FEV_1). FEV_1 is the standard for measuring lung function in CF patients, which is associated with pulmonary outcomes and general morbidity and mortality.[3] Pulmonary exacerbations are also considered to be associated with reduced lung function and mortality and therefore can be an important indirect measurement of pulmonary function.[4] The Cystic Fibrosis Questionnaire-revised (CFQ-R) is a validated patient-reported outcome questionnaire specific to CF which focuses on respiratory health perception, quality of life, and clinically relevant respiratory symptoms.[3] A minimally clinically important difference of 4 points was established for this domain.[5] Weight is an important secondary outcome as studies have shown that lower than average birth weights and poor growth are correlated with lower lung function, increased morbidity and mortality in children with CF.[3]

Approval of ivacaftor was based on two phase III, randomized, double-blind, placebo controlled studies; STRIVE (published) and ENVISION (unpublished).[6,7] Studies included patients with CF and the G551D mutation on at least one CFTR allele. The main difference between the studies was STRIVE included patients 12 years and older with an average age of 26 and ENVISION enrolled patients 6 to 11 years with an average age of 9. STRIVE was a good quality study that showed that there was moderate strength of evidence that ivacaftor was more effective than placebo (mean absolute treatment difference in percent predicted FEV_1 was 10.6%, 95% CI 8.6 to 12.6, $p<0.001$).[6] ENVISION was not published and therefore did not meet our study inclusion criteria of being peer reviewed. However, results from ENVISION were similar to STRIVE suggesting a similar level of efficacy in patients 6 to 11 years (mean absolute treatment difference in percent predicted FEV_1 was 12.5%, $p<0.0001$).[7]

Safety: Ivacaftor was well tolerated with lower rates of discontinuation compared to placebo, 1% and 5%, respectively.[6] Increased hepatic enzymes were the cause of drug discontinuation and the manufacturer recommends that they be monitored throughout treatment. The most common adverse events experience with ivacaftor include; headache (24%), oropharyngeal pain (22%), upper respiratory tract infection (22%), nasal congestion (20%), abdominal pain (16%), nasopharyngitis (15%) and diarrhea (13%).[1] Severe adverse events occurring more often with ivacaftor were abdominal pain, increased hepatic enzymes and hypoglycemia.[1] Ivacaftor is metabolized by CYP3A enzymes and should not be given with strong CYPf3A inducers due to reductions in ivacaftor exposure which may reduce effectiveness.[1]

BACKGROUND/CURRENT LANDSCAPE

CF is a genetic disease which can affect multiple organs, in which lung disease is responsible for approximately 85% of the mortality. The effects on the lungs are characterized by dehydration of the airway surface liquid and impaired mucociliary clearance which leads to chronic pulmonary infection.[2] Available treatments for CF include aerosolized antibiotics, dornase alfa, hypertonic saline, oral corticosteroids, inhaled corticosteroids, oral nonsteroidal anti-inflammatory drugs, macrolide antibiotics, inhaled bronchodilators (β-agonists and anticholinergic medications) and oral antistaphylococcal antibiotics.[2] Recommendations for treatment are often based on the severity of lung disease, defined by forced expiratory volume (FEV_1) percentage of predicted (Table 1).

Table 1. Categorization of lung function based on FEV_1 percentage of predicted[2]

Category	Percentage of Predicted
Normal	>90% predicted
Mildly impaired	70-80% predicted
Moderately impaired	40-69% predicted
Severely impaired	<40% predicted

The 2007 Cystic Fibrosis Foundation Pulmonary Guidelines outlines treatment recommendations for chronic maintenance of lung health in CF patients. Using the U.S. Preventive Services Task Force recommendation grades, chronic treatments are given an evidence grade as well as an estimated treatment effect (Table 2). In CF patients with moderate to severe lung disease, inhaled tobramycin, dornase alfa and macrolide antibiotics (for all levels of disease) have been shown to provide substantial benefit in improvement in lung function.[2]

Several Cochrane reviews evaluated treatments options for patients with CF. Their findings suggests improved lung function as a result of inhaled tobramycin, hypertonic saline, dornase alfa, macrolide antibiotics and inhaled $beta_2$ agonists.[8-12] They found no benefit with inhaled corticosteroids and insufficient evidence to support oral nonsteroidal use.[13,14] Oral steroids did provide some benefit but were associated with high rates of adverse events.[15]

Table 2. Cystic Fibrosis Pulmonary Guidelines for Chronic CF Treatment[2]

Treatment	Estimated Benefit	Mean Changes in FEV1*	Strength of Recommendation
Inhaled tobramycin (moderate-severe lung disease)	Substantial	7.8% - 12.0%	Good
Dornase alfa (moderate-severe lung disease)	Substantial	5.8% - 7.3%	Good
Inhaled tobramycin (asymptomatic-mild disease)	Moderate	No change	Fair
Dornase alfa (asymptomatic-mild disease)	Moderate	3.2%	Fair
Hypertonic saline	Moderate	3% - 7.7%	Fair
Oral NSAIDS	Moderate	Slowed rate of decline	Fair
Macrolide antibiotics	Substantial	3.65 – 6.2%	Fair
Inhaled Beta2 agonists	Moderate	-	Good

* Not head-to-head trials comparisons.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints

All Studies:
- Change in forced expiratory volume (FEV_1)
- Pulmonary exacerbations (days in hospital/ days on antibiotics)
- Cystic Fibrosis Questionnaire-revised Score
- Weight Change
- All-cause Mortality

Study Endpoints:

STRIVE:
- Change in forced expiratory volume (FEV_1)
- Pulmonary exacerbations
- Cystic Fibrosis Questionnaire-revised score
- Sweat chloride concentrations
- Weight Change

Evidence Table

Ref./ Study Design[1]	Drug Regimens	Patient Population	N	Duration	Efficacy Results[2] (CI, p-values)	ARR / NNT[3]	Safety Results^ (CI, p-values)	ARR/ NNH[3]	Quality Rating[4]; Comments
STRIVE[6]									
Ramsey, et al Design: International, DB, PC,RCT, phase III	1. Ivacaftor 150 mg every 12 hours 2. Placebo	Average Age: 26 years <18 years: 22% ≥ 18 years: 78% Male: 48% Baseline FEV_1: 63.6% <70% FEV_1 predicted: 58% ≥ 70% FEV_1 predicted: 42% Sweat chloride: 100.2 mmol/L <u>Inclusion:</u> Patients ≥12 year old with CF, G551D mutation on at least one CFTR allele and FEV1 of 40 to 90% of predicted value. <u>Exclusion:</u> Ongoing illness, pulmonary exacerbation or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks of start; abnormal liver or renal function,	1. 84 2. 83	48 weeks (evaluated at 24 and 48 weeks)	**Primary:** <u>FEV_1% predicted absolute change from baseline (mean) at week 24:</u> Ivacaftor (83): 10.4 Placebo (78): -0.2 Tx effect: 10.6% 95% CI 8.6 to 12.6, p < 0.0001 **Secondary:** <u>FEV_1% predicted absolute change from baseline (mean) at week 48:</u> Ivacaftor (83): 10.1 Placebo (78): -0.4 Tx effect: 10.5% 95% CI 8.5 to 12.5, p<0.0001 <u>Pulmonary exacerbation at 48 weeks:</u> Ivacaftor (28): 33.7% Placebo (44): 56.4% RR: 0.43 p= 0.0003 95% CI 0.27 to 0.68 <u>Mean absolute change from baseline in CFQ-R at week 48</u>: Ivacaftor (74): 5.9	ARR= 22.7% NNT= 4.41	<u>Discontinuation due to AE</u>: Ivacaftor: 1 (1%) Placebo: 4 (5%) ARR: 0.04 95% CI -0.02 to 0.11 <u>Severe AE:</u> Ivacaftor: 20 (24%) Placebo: 33 (42%) ARR: 0.18 95% CI 0.04 to 0.32	NA NA	• Good Quality • Internal Validity Review of Bias:: <u>Selection:</u> low bias; clear randomization and allocation concealment <u>Performance</u>: low bias.; blinding of patients and care givers. <u>Detection</u>: low bias.; study monitors blinded. <u>Attrition</u>: low attrition; ITT analysis. • Subgroup analysis performed for baseline FEV1, geographic region, sex, and age which revealed similar significant treatment results. • Changes in sweat chloride concentrations have not been correlated to clinically meaningful outcomes and therefore not reported. • Patients allowed to continue pre-study medications.

		history of prolonged QT/QTc interval, transplantation history, colonization with organisms associated with a more rapid decline in pulmonary status (e.g., *B. cenocepacia, B. dolosa,* and *M. abcessus*), concomitant use of inhibitors/inducers of CYP3A4 or use of inhaled hypertonic saline treatment (required to stop inhaled 4 weeks prior to first dose of study drug).			Placebo (62): -2.7 Treatment effect: 8.6 P<0.001 <u>Mean change from baseline in weight (kg) at 48 weeks:</u> Ivacaftor (77): 3.1 Placebo (68): 0.4 Treatment effect: 2.7kg P<0.001				

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover, FAS = full analysis set data, LOCF= last observation carried forward.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
Clinical Abbreviations: CFQ-R=Cystic Fibrosis Questionnaire-revised

CLINICAL EFFICACY-

Ivacaftor was approved by the FDA in January of 2012 on the basis of two phase III studies, STRIVE (published) and ENVISION (unpublished).[1,5] Both studies were randomized, double-blind, placebo controlled trials comparing ivacaftor 150mg twice daily to placebo with evaluations at 24 and 48 weeks. Inclusion criteria for both studies was a diagnosis of CF, G551D mutation on at least one CFTR allele and a FEV_1 of 40-90% (STRIVE) and 40-105% (ENVISION) of the predicted value for persons of their age, sex and height. STRIVE enrolled patients 12 years of age and older where ENVISION included patients 6 to 11 years. In both studies patients were allowed to continue on pre-study medications with the exception of hypertonic saline treatments. The primary outcome in both trials was the FEV_1% predicted absolute change from baseline at week 24.[6,7]

STRIVE was a good quality study enrolling 167 patients with an average age of 25 years and baseline FEV_1 of 64%.[6] There was moderate strength of evidence that ivacaftor was superior to placebo in improving FEV_1 at 24 weeks (mean absolute treatment effect 10.6%, 95% CI 8.6 to 12.6, $p<0.001$). This effect was sustained at 48 weeks with similar statistically significant results. The percentage of patients experiencing a pulmonary exacerbation at 48 weeks was higher for placebo than ivacaftor; with an ARR of 22.7% and NNT of 4.41. Ivacaftor was also shown to be statistically superior to placebo in the outcomes of weight gain and improvements on the respiratory symptom scale (Cystic Fibrosis Questionnaire). Benefits of ivacaftor were also shown in analyses of subpopulations regardless of age, gender, disease severity or geographic region. There was moderate strength of evidence that ivacaftor was well tolerated with discontinuation rates less than placebo, 1% and 5%, respectively.

ENVISION was not graded because it was not published and therefore did not meet our inclusion criteria for being peer reviewed. Results are presented for information purposes, as this study is the only study in patients under 12. Ivacaftor (n=26) was found to be superior to placebo (n=26) for mean absolute change in percent predicted FEV_1 through 24 weeks, difference of 12.5% ($p<0.0001$).[7]

Limitations associated with STRIVE and ENVISION include small sample sizes (common in studies of orphan diseases) and study durations lasting 48 weeks. Only patients with the G551D mutation have been shown to benefit with ivacaftor treatment. A study by Flume et al, was done in homozygous patients for the F508del-CFTR mutation which showed no benefit in lung function or patient-reported outcomes.[16] The FDA summary review of ivacaftor found efficacy results to be “robust”. Additional data on long term efficacy is being obtained in an ongoing open-label extension study (PERSIST).[17]

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APPENDIX 1: SPECIFIC DRUG INFORMATION

CLINICAL PHARMACOLOGY[1]

Ivacaftor works by potentiating the G55ID-CFTR protein, which facilitates increased chloride transport by increasing the time that activated CFTR channels at the surface of the cell are open. This effect translates into assistance in regulating salt and water absorption and secretion throughout the body. The CFTR protein can be found on the epithelial cells in multiple organs including the lungs, pancreas, sweat glands and gastrointestinal tract.

PHARMACOKINETICS[1]

Parameter	Result
Absorption	increased 2- to 4-fold when given with food containing fat
Protein Binding	approximately 99% bound to plasma proteins
Elimination	87.8% in feces
Half-Life	12 hours
Metabolism	hepatic via CYP3A to M1 and M6*

* M1 has approximately one-sixth the potency of ivacaftor and is considered pharmacologically active. M6 isn't pharmacologically active.

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications): None known.

Cautions: Ivacaftor has been shown to cause elevated transaminases. Liver function tests should be done at baseline and every three months for the first year of therapy and annually for following years. Concomitant use with CYP3A inducers may reduce ivacaftor concentrations and reduce effectiveness and therefore this combination is not recommended.

Adverse Effects: Adverse effects occurring in more than 8% of study patients were headache, oropharyngeal pain, upper respiratory tract infection, nasal congestion, abdominal pain, nasopharyngitis, diarrhea, rash, nausea and dizziness (Table 4). Severe adverse events occurring more often with ivacaftor were abdominal pain, increased hepatic enzymes and hypoglycemia.[1]

Table 4. Incidence of Adverse Drug Reactions in ≥8% of KALYDECO-Treated Patients with a *G551D* Mutation in the *CFTR* Gene and Greater than Placebo in 2 Placebo-Controlled Phase 3 Clinical Trials of 48 Weeks Duration [1]

Adverse Reaction (Preferred Term)	Incidence: Pooled 48-week Trials	
	KALYDE	Placebo N=104 n (%)

	CO N=109 n (%)	
Headache	26 (24)	17 (16)
Oropharyngeal pain	24 (22)	19 (18)
Upper respiratory tract infection	24 (22)	14 (14)
Nasal congestion	22 (20)	16 (15)
Abdominal pain	17 (16)	13 (13)
Nasopharyngitis	16 (15)	12 (12)
Diarrhea	14 (13)	10 (10)
Rash	14 (13)	7 (7)
Nausea	13 (12)	11 (11)
Dizziness	10 (9)	1 (1)

Tolerability (Drop-out rates, management strategies): Ivacaftor was well tolerated with discontinuation rates less than placebo, 1% and 5%, respectively.[6]

Pregnancy/Lactation rating: Pregnancy category B, use only if clearly indicated. Ivacaftor excretion into milk is probable.

Unanswered safety questions: The safety and efficacy of ivacaftor beyond one year is unknown. Elevated transaminase levels experienced in small study populations may become more problematic when used in a large number of patients. The safety and efficacy in children under 6 and in individuals with other CF mutations has not been studied at this point.

Lab Tests: Elevated transaminases have been reported with ivacaftor treatment and monitoring of ALT and AST is recommended prior to therapy initiation and every 3 months during the first year and then annually. It is recommended that ivacaftor is discontinued if ALT or AST is 5 times the upper limit of normal. In studies two patients in the ivacaftor group experienced a serious adverse reaction of elevated liver transaminases compared to none in the placebo group.

Dose Index (efficacy/toxic): No overdoses have been reported. Doses up to 800mg were studied without any adverse events.

Look-alike / Sound-alike (LA/SA) Error Risk Potential: LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexi-Comp	ISMP	Clinical Judgment

LA/SA for invacaftor (generic)	None	None	Indinivir Invirase
LA/SA for Kalydeco (brand)	None	None	Kalbitor Kaletra

DOSE & AVAILABILITY[1]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Ivacaftor 150mg	Tablet	Oral	150 mg every 12 hours	Not studied. No dose adjustments are recommended for patients with mild to moderate renal impairment. Caution is advised when ivacaftor is used in patients with severe renal impairment (CrCl ≤30 mL/min) or end stage renal disease.	No dose adjustment for mild hepatic disease. 150mg once daily is recommended for patients with moderate (Child-Pugh Class B) hepatic impairment. Caution is advised when used in patients with severe hepatic impairment (Child-Pugh class C) and a dose of 150mg daily or less is recommended.	150 mg every 12 hours	Not studied	Must be taken with fat-containing food .

ALLERGIES/INTERACTIONS[1]

Drug-Drug: Ivacaftor is metabolized via CYP3A and therefore co-administration with other strong CYP3A inhibitors increases ivacaftor concentrations. It is recommended that ivacaftor dose be reduced to 150mg twice weekly if combined with a strong CYP3A inhibitor, for example ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin and clarithromycin. For moderate CYP3A inhibitors (fluconazole and erythromycin) it is recommended that the dose be decreased to 150mg of ivacaftor once daily. Strong CYP3A inducers (rifampin, rifabutin,

phenobarbital, carbamazepine, phyenytoin and St.John's Wort) may decrease ivacaftor concentrations and therefore it is not recommended. ivacaftor and its metabolite may inhibit CYP3A and P-gp, causing increases in exposure to drugs that are substrates of CYP3A and/or P-gp. Use ivacaftor cautiously in patients on CYP3A and/or P-gp subtrates such as digoxin, cyclosporine and tacrolimus. When ivacaftor is used with CYP2C9 substrates monitoring is recommended (i.e. warfarin).

Food-Drug: Ivacaftor should not be taken with grapefruit or Seville oranges due to possible increased exposure to ivacaftor.

Allergy/Cross Reactive Substances: None known.

APPENDIX 2: Suggested PA Criteria

Ivacaftor (Kalydeco)

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which the drug has been shown to be effective and safe.

Length of Authorization: 6 months.

Approval Criteria

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Does the client have a diagnosis of cystic fibrosis and is 6 years of age or older?	Yes: Go to #3.	No: Pass to RPH; Deny (medical appropriateness)
3. Does the patient have a documented G551D mutation in the CFTR gene? • If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the *G551D* mutation.	Yes: Go to #4.	No: Pass to RPH; Deny (medical appropriateness)
4. Is the request from a practitioner at an accredited Cystic Fibrosis Center or a pulmonologist?	Yes: Go to #5	No: Pass to RPH; Deny (medical appropriateness)
5. Is the patient on ALL or has had an adequate trial, if indicated and/or tolerated of the following medications below: - Dornase alfa (Pulmozyme®) AND - Hypertonic saline (Hyper-Sal®) AND - Inhaled or oral antibiotics (if appropriate)	Yes: Go to #6	No: Pass to RPH; Deny (medical appropriateness)
6. Is the prescription for ivacaftor 150mg twice daily, once daily or twice-a-week?	Yes: Approve for 6 months	No: Pass to RPH; Deny (medical appropriateness)

Renewal Criteria		
1. Is this the first time the patient is requesting a renewal?	Yes: Go to #2	No: Go to #3
2. Does the patient have documented response to therapy? Document response (e.g. improvement in FEV1, weight gain, reduction in exacerbations or sweat test).	Yes: Go to #3	No: Pass to RPH; Deny (medical appropriateness)
3. Has the patient been compliant with therapy, as determined by refill claims history or as reported by the requestor?	Yes: Go to #4	No: Pass to RPH; Deny
4. Is the prescription for ivacaftor 150mg twice daily, once daily or twice-a-week?	Yes: Approve for 6 months	No: Pass to RPH; Deny (medical appropriateness)

Limitations of Use:

• Ivacaftor is not effective in patients with Cystic Fibrosis who are homozygous for the *F508del* mutation in the *CFTR* gene.
• Ivacaftor has not been studied in other populations of patients with Cystic Fibrosis.

P&T Action: 6/28/12(KS), 4/26/12 (MH/KS)
Revision(s):
Initiated: