Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Policy Update: Ivacaftor (Kalydeco®) for Cystic Fibrosis

Month/Year of Review: May 2015 **Last Reviewed**: May 2014

Current PA Criteria:
See **Appendix 3**. Prior authorization (PA) criteria are in place to ensure appropriate drug use and limit to patient populations in which ivacaftor has demonstrated to be effective and safe.

Research Questions:

- Does new evidence for efficacy or harms change previous conclusions regarding the effectiveness and safety of ivacaftor?
- Are there unique patients or situations where ivacaftor may be more effective or safer than currently available agents?

Conclusions:

- There is insufficient to low quality evidence that ivacaftor does not significantly improve lung function in patients with Cystic Fibrosis (CF) with the *R117H* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, as measured by lack of improvement in percent-predicted FEV_1 compared to placebo (2.6% vs. 0.5%, respectively; p=0.19) based on one small, unpublished study. However, a post hoc subgroup analysis of adults 18 years of age or older showed a statistically significant improvement in FEV_1 compared to placebo (4.5% vs. -0.5%; p=0.01). However, a subgroup of patients aged 6 to 11 years demonstrated an unexplained negative effect, as absolute FEV_1 was significantly lower than placebo by 6.5% points (p=0.03). Based on this evidence alone, the FDA approved use of ivacaftor in adults with the *R117H* mutation based on this subgroup analysis. The FDA approved use of ivacaftor in pediatric patients 6 years of age and older based on an open-label extension study which subsequently showed a 6.4% improvement in mean change in FEV_1.
- There is insufficient to low quality evidence, based on one small pharmacokinetic study and one safety study in pediatric CF patients' aged 2 to 5 years (32 patients with the *G551D* mutation and 2 patients with the *S549N* mutation), that ivacaftor is relatively safe and improves sweat chloride concentrations. Based on this evidence alone, the FDA approved ivacaftor in patients aged 2 to 5 years with all of the following mutations: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R* or *R117H*.
- Evidence to support use of ivacaftor based on clinical outcomes remains very limited, with very small studies dealing with disease mutations that affect a small number of patients in the United States. It is difficult to determine the overall effectiveness and safety of ivacaftor for the treatment of CF and how it will affect disease progression. The strongest evidence remains in patients with the *G115D* mutation.

Author: M. Herink, Pharm.D. Date: May 2015

Ivacaftor should not be used in CF patients homozygous for the *F508del* mutation (the most common mutation) due to evidence for lack of benefit in this population.

Recommendations:

- Limited, inconsistent, and unpublished evidence at this time prohibits adequate and fair evaluation of the efficacy of ivacaftor for the new FDA-approved indications. It is prudent to further await published data supporting statistically significant improvements in FEV_1, or other clinically relevant outcomes, in patients with the R117H mutation in the CFTR gene and in pediatric patients aged 2 to 5 years before approving use in these populations.

Reason for Review:

Since the last P&T review of ivacaftor, the FDA approved ivacaftor for the treatment of CF in patients age 6 years and older who have an *R117H* mutation in the *CFTR* gene. In addition, the FDA approved ivacaftor for children aged 2 to 5 years who have one of the 10 FDA-approved mutations in the CFTR gene. Ivacaftor was already approved for people aged 6 years and older with these mutations. This review will evaluate the new indications and supporting evidence.

Previous Recommendations:

- There is low to moderate level of evidence to suggest that ivacaftor is superior to placebo in patients (≥12 years old) with the G551D mutation, as illustrated by an increase in forced expiratory flow rate at one second (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.
- 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 and important clinical outcomes including pulmonary exacerbations and hospitalizations are unknown.
- It is recommended to use clinical prior authorization criteria (**Appendix 3**) 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.
- There is insufficient to low quality evidence based on one unpublished, phase III trial, that in addition to CF patients with the G551D mutation, ivacaftor is more effective than placebo in improving lung function as measured by FEV_1 in patients with 8 additional mutations. These include: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P and G1349D. Evidence does not support use of the drug in patients with the G970R mutation.

Background:

Cystic Fibrosis (CF) is a genetic disease that can affect multiple organs, of which progressive lung disease is responsible for approximately 85% of mortality observed in this population.[1] Most available treatments for CF focus on symptom management and treatment of chronic infection, including antibiotics, dornase alfa, hypertonic saline, inhaled corticosteroids, oral nonsteroidal anti-inflammatory drugs, and inhaled bronchodilators.[2] Important outcomes for treatment include reducing mortality, pulmonary exacerbations, and respiratory symptoms. Forced expiratory volume in one second (FEV_1) is a commonly used outcome in clinical trials. The Cystic Fibrosis Questionnaire-revised (CFQ-R) is a validated patient-reported outcome questionnaire specific to CF which focused on respiratory health perception, quality of life, and clinically relevant respiratory symptoms. A minimally clinically important difference of 4 points was established for this domain.[3] Weight is also a commonly measured secondary outcome in trials of CF patients, as studies have shown that lower than average birth weights and poor growth are correlated with poorer lung function, increased morbidity and mortality in children with CF. [3] Sweat chloride levels is the gold standard for a diagnosis of CF. Normal individuals typically have levels < 40 mmol/L and patients with CF have elevated levels > 60 mmol/L.[4] More recently, sweat chloride has been used as a biomarker for evaluating changes in the CFTR activity in clinical trials of ivacaftor.[5] However, there is no evidence that sweat chloride is correlated with meaningful clinical benefits and it has shown to correlate with improvement in FEV_1. [4]

Many different mutations have been identified in the gene that causes CF. Ivacaftor is a CF transmembrane conductance regulator (CFTR) potentiator approved by the FDA in 2012 for the treatment of CF in patients 6 years and older with the G551D mutation in the CFTR gene (approximately 4% of CF patients) by demonstrating statistically superior improvement in FEV_1 compared to placebo.[6–9] Ivacaftor is proposed to treat the underlying cause of CF, by influencing the basic gene defect, by normalizing airway surface liquid and helping to re-establish mucociliary clearance.[10,11] Ivacaftor is now indicated for the treatment of CF in patients in patients' aged 2 years and older who have one of the following mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, R117H.* Over 1900 mutations have been identified in the CFTR gene. Patients homozygous for the *F508*del CFTR mutation, the most common mutation in the CFTR gene accounting for approximately two thirds of mutations, do not receive benefit in lung function or patient-reported outcomes with ivacaftor and the drug should not be used in this population.[12]

There are no head-to-head trials comparing ivacaftor to other CF treatments. Changes in FEV_1 observed with ivacaftor are similar to other therapies used in the chronic management of CF.

Elevated transaminases should be assessed prior to initiating ivacaftor and every 3 months during the first year of treatment. Patients who develop increased transaminase levels should be closely monitored. Therapy should be stopped if increases in ALT or AST greater than 5-times the upper limit of normal are observed.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls were conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

A Cochrane Collaboration Systematic Review was completed to evaluate the effects of CFTR potentiators on clinically important outcomes in children and adults with cystic fibrosis.[11] RCTs comparing CFTR potentiators to placebo were included in the review. At the time of this review, it had only been studied in those with the *G55aD* and *F508del* mutations, thus limiting the current relevance of the results. Primary outcomes were survival, quality of life, and change in FEV_1 from baseline. There were many secondary outcomes.

Four RCTs of parallel design (n=378) were included in the review, two of which have been published. Vertex Pharmaceuticals Incorporated sponsored all trials. Three trials included participants with the *G551D* mutation (one phase 2 and two phase 3) in adults and pediatrics, while one trial was in the *F508del* mutation. The primary endpoints in the trials were safety and/or FEV_1. There was a high risk of selective reporting bias and attrition bias in the included studies, with an overall moderate risk of bias across the included trials.[11]

No trial reported any deaths. Significantly higher quality of life scores in the respiratory domain were reported by the adult phase 3 G551D trial at 24 weeks, mean difference 8.10 (95% confidence interval (CI) 4.77 to 11.43) and 48 weeks, mean difference 8.60 (95%CI 5.27 to 11.93); but not by the pediatric phase 3 G551D trial. At 24 weeks in the 3 *G551D* trials, both children and adults in the ivacaftor group reported significant improvements in the change from baseline in FEV_1, with a mean difference of 16.8% (95% CI 13.5-20.1), or 0.37 liters at 48 weeks. At 16 weeks in the *F508* trial, there was no difference in FEV1 between ivacaftor and placebo (mean difference 2.4%; 95% CI -0.95 to 5.75). One study in adults with the *G551D* mutation reported significantly fewer episodes of pulmonary exacerbation requiring hospitalization in the ivacaftor group (OR 0.37; 95% CI 0.16 to 0.81).[11] Pooling data from the two of the G551D trials showed no statistical difference in number of pulmonary exacerbation (OR 0.64; 95% CI 0.36 to 1.12) or adverse effects requiring drug discontinuations (OR 0.25; 95% CI 0.04 to 1.56). [11]

The authors concluded that the *G551D* phase 3 trials demonstrated a clinically relevant impact at 24 and 48 weeks in adults and children but that there is no evidence to support ivacaftor in patients with the *F508del* mutation. [11]

New Guidelines:
No relevant guidelines were identified.

New FDA Approved Indications:
In December 2014, the FDA approved the use of ivacaftor for use in subjects with the *R117H* mutation in the CFTR gene. The *R117H* mutation is the third most common mutation, present in approximately 4% of people with CF, or approximately 700 people in the United States. This approval was based on the Phase 3, double-blind, randomized unpublished KONDUCT study in subjects aged 6 years and older.[9,13] The primary outcome was absolute change from baseline in percent (%)-predicted FEV_1 through week 24. Those with a %-predicted FEV_1 40-90% for subjects aged 12 years or older or 40-105% for subjects aged 6 to 11 years were included. A total of 70 subjects were randomized (34 in the ivacaftor group and 35 in the placebo group) and the majority of subjects were 18 years or older (72%). There was an absolute change from baseline in %-predicted FEV_1 of 2.6% in the ivacaftor group compared to 0.5% in the placebo with a least squares mean difference of 2.1% (95% CI -1.13 to 5.35%). This difference was not statistically significant (p=0.19) and therefore the study did not meet its primary endpoint. There was also no significant difference in time to first pulmonary exacerbation (p=0.8556) or change from baseline in body mass index (BMI) at week 24 (p=0.78). There was a statistically significant difference in change in FEV_1 relative to placebo in a subgroup of subjects aged 18 years and older (4.5% vs. -0.5%, respectively; p=0.01), which represented approximately 75% of subjects. In addition, there was a statistically significant difference in change in FEV_1 relative to placebo in subjects with the 5T poly-T status (6% vs. 0.7%; treatment difference 5.3; 95% CI 1.3 to 9.3), though subjects with 7T status only did not show a statistically significant difference in FEV_1 compared to placebo (-0.7% vs. -0.9%; treatment difference 0.2% [95% CI -8.1 to 8.5%]). However, the mean absolute change in FEV_1 in the subgroup of 17 subjects aged 6 to 11 years was significantly lower compared to placebo (-2.8% vs. 3.5%), demonstrating an unexplained negative effect in children. The company concluded that this was driven by the high baseline FEV_1 for these patients and the small sample size and that there was an overall neutral effect on lung function. There was a significantly greater decrease in sweat chloride in the ivacaftor group compared to placebo (-26.3 mmol/L vs. -2.3 mmol/L; p<0.0001)[13]; however there are no data available in patients aged 12 to 17 years. An unpublished, open-label extension period study (KONTINUE) showed an improvement in FEV_1 of 6.4% in the subgroup of 6 to 11 year olds. The initial decrease in the controlled trial should be taken into consideration and more evidence is needed to demonstrate an improvement. Results for KONTINUE were not available on clinicaltrials.gov.

Although the study did not meet the primary endpoint, adult approval was based on subgroup analysis from the trial and expected clinical benefit based on secondary outcomes in pediatric patients.

In March 2015, the FDA approved ivacaftor for use in children ages 2 to 5 years with CF who have one of the 10 mutations in the CFTR gene already approved in adults (*G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, and R117H*).[9] The expanded use in this population is based on results of an open-label, non-controlled, phase 3 study (KIWI) that evaluated the safety and pharmacokinetics of weight-based dosing of ivacaftor (50 mg or 75 mg twice daily) for 24 weeks. A total of 9 patients, all with the *G551D* mutation in the CFTR gene, were enrolled in the initial pharmacokinetic stage of the study. Pharmacokinetic properties for both doses were similar to that reported in adults in previous studies. The second part of the study, which included 32 patients with the *G551D* mutation and 2 patients with the *S549N* mutation, assessed safety outcomes over 24 weeks. Overall, 88.9% of patients experienced at least one adverse event; the most common being pyrexia, vomiting, ecchymosis, and

rhinorrhea. Five patients experienced elevations in liver transaminases and there were a total of 7 serious adverse events. There was a decrease in the sweat chloride concentration through week 24 (-46.86 mmol/L) but statistical analysis compared to placebo was not provided and other clinical efficacy outcomes, such as lung function, were not included.[14]

Randomized Controlled Trials:

The only relevant RCT identified was the KONNECTION trial.[15] This trial data were previously presented and reviewed by the P&T committee to support the expanded indication; however, it was unpublished at the time. A summary of the trial can be found below, with the abstract presented in **Appendix 1**.

Table 1. Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results	Quality*
KONNECTION[15] Randomized, Crossover study	Ivacaftor 150 mg BID vs. placebo	Patients with CF ≥6 years old with non-*G551D* gating mutations (*G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P,* or *G1349D.* (N=39)	Absolute change in %-predicted FEV_1 through 8 weeks of treatment	Ivacaftor: 7.5% Placebo: -3.2% Mean difference: 10.7% (95% CI 7.3 to 14.1; P<0.0001) There was high variability among and within subgroups of genotypes; in many groups, FEV_1 did not significantly change from baseline and the number of patients in each subgroup was extremely small.	Poor

Abbreviations: BID = twice daily; CF = Cystic Fibrosis; FEV1 = Forced expiratory volume in 1 second;
*Quality of each study is ranked as "Good", "Fair" or "Poor" based on DURM Standard Methods for Quality Assessment and Grading the Evidence.

References:

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3. Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic Pseudomonas aeruginosa airway infection. *Chest*. 2009;135(6):1610-1618. doi:10.1378/chest.08-1190.
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11. Patel S, Sinha IP, Dwan K, Echevarria C, Schechter M, Southern KW. Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. *Cochrane Database Syst Rev*. 2015;3:CD009841. doi:10.1002/14651858.CD009841.pub2.
12. Flume PA, Liou TG, Borowitz DS, et al. Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. *Chest*. 2012;142(3):718-724. doi:10.1378/chest.11-2672.
13. ClinicalTrials.Gov. Study of Ivacaftor in Subjects with Cystic Fibrosis Who Have the R117H-CF Transmembrane Conductance Regulator Mutation (KONDUCT). https://clinicaltrials.gov/ct2/show/NCT01614457. Accessed April 15, 2015.
14. ClinicalTrials.Gov. Study of Ivacaftor in Cystic Fibrosis Subjects 2 Through 5 Years of Age with a CFTR Gating Mutation. ClinicalTrials.Gov Identifier: NCT01705145. https://clinicaltrials.gov/ct2/show/NCT01705145?term=KIWI+study&rank=2. Accessed April 27, 2015.
15. De Boeck K, Munck A, Walker S, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. *J Cyst Fibros*. 2014;13(6):674-680. doi:10.1016/j.jcf.2014.09.005.

Author: M. Herink, Pharm.D. Date: May 2015

Appendix 1: Abstracts of Clinical Trials

1. De Boeck K1, Munck A2, Walker S3, Faro A4, Hiatt P5, Gilmartin G6, Higgins M6. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. *J Cyst Fibros*. 2014 Dec;13(6):674-80. doi: 10.1016/j.jcf.2014.09.005. Epub 2014 Sep 26.

BACKGROUND:
Ivacaftor is used to treat patients with CF and a G551D gating mutation; the KONNECTION study assessed the efficacy and safety of ivacaftor in patients with CF and a non-G551D gating mutation.

METHODS:
Patients with CF ≥6-years- old with non-G551D gating mutations received ivacaftor 150mg q12h or placebo for 8weeks in this 2-part, double-blind crossover study (Part 1) with a 16-week open-label extension (Part 2). The primary efficacy outcome was absolute change in FEV1 through 8 and 24weeks of ivacaftor treatment; secondary outcomes were changes in BMI, sweat chloride, and CFQ-R and safety through 8 and 24weeks of treatment.

RESULTS:
Eight weeks of ivacaftor resulted in significant improvements in percent predicted FEV1, BMI, sweat chloride, and CFQ-R scores that were maintained through 24weeks. Ivacaftor was generally well tolerated.

CONCLUSIONS:
Ivacaftor was efficacious in a group of patients with CF who had selected non-G551D gating mutations.

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions
1 ivacaftor.mp 65
2 Kalydeco.mp 11
3 cystic fibrosis.mp. or Cystic Fibrosis/ 23507
4 1 or 2 65
5 3 and 4 65
6 limit 5 to yr="2014-Current" 21
7 Limit 6 to (clinical trial or controlled clinical trial or meta analysis or practice guideline or randomized controlled trial or systematic reviews) 2

Both of the resulting two studies were published in March 2014 and were included in the previous update.

Appendix 3: Current PA Criteria

Ivacaftor (Kalydeco®)

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which ivacaftor has demonstrated to be effective and safe.

Length of Authorization: 6 months

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, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene?	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 the following drugs, or has had an adequate trial of each drug, unless contraindicated: - 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 ivacaftor dosed at no more than 150 mg twice daily (or appropriately dosed based on drug-drug interactions)?	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	Yes: Go to #3	No: Pass to RPH; Deny (medical

response to therapy? Document response (e.g. improvement in FEV_1, weight gain, reduction in exacerbations or sweat test).		appropriateness)
3. Has the patient been compliant with therapy, as determined by refill claims history or as reported by requestor?	Yes: Go to #4	No: Pass to RPH; Deny
4. Is ivacaftor dosed no more than 150 mg twice daily (or appropriately dosed based on drug-drug interactions)?	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 adequately studied in populations with other mutations of the CFTR gene.

P&T Action: 5/15 (MH), 5/14, 6/12, 4/12
Revision(s): TBD
Initiated: