Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for ivacaftor when it is determined to be medically necessary because the criteria shown below are met.

**When Policy Topic is covered**

Ivacaftor may be considered **medically necessary** when ALL of the following criteria are met:

- Patient is 2 years or older; AND
- Patient has a documented diagnosis of cystic fibrosis (CF); AND
- Patient is not homozygous for the F508del mutation in the CFTR gene.

**Usual Dosing:** Ivacaftor is to be administered with fat-containing food

- Adults and pediatric patients age 6 years and older: one 150 mg tablet taken orally every 12 hours
- Pediatric patients age 2 through 5 years:
  - Weighing 14kg or more: 75mg granule packet by mouth every 12 hours
  - Weighing less than 14kg: 50mg granule packet by mouth every 12 hours

Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary. Use of ivacaftor with strong CYP3A inducers, such as rifampin, substantially decreases the exposure of ivacaftor, which may reduce the therapeutic effectiveness of ivacaftor.

**When Policy Topic is not covered**

Ivacaftor is considered **not medically necessary** when used for all other conditions, including but not limited to:

- Cystic fibrosis patients younger than 2 years old – as the safety and efficacy of ivacaftor has not been studied in this population;
- Cystic fibrosis patients with unknown CFTR gene mutation(s);
- Cystic fibrosis patients with gene mutations other than those listed above, including patients homozygous for the F508del mutation.
Considerations
Ivacaftor requires prior authorization through the pharmacy services department. Initial approval is for 6 months. When prior authorization is approved, ivacaftor may be authorized in quantities of 120 tablets per 30 days and must be obtained from a network specialty pharmacy. Continuation of therapy will be considered if the member has improvement in FEV1, improvement in CF symptoms, decrease in sweat chloride concentration, or stabilization of disease.

Description of Procedure or Service
Cystic Fibrosis

Cystic fibrosis is an autosomal recessive genetic disorder that causes thick, sticky mucus to build up in the lungs, digestive tract, and other areas of the body. It affects approximately 30,000 children and adults in the United States, and approximately 36,000 children and adults in Europe. Approximately one in 3,500 children in the United States is born with CF each year. All ethnic and racial groups are affected, although CF is most common in Caucasians. It is one of the most common chronic lung diseases in children and young adults and is considered a life-threatening disorder. Survival has increased for patients with cystic fibrosis from the late teens to the mid-30s due in part to the many medical advances in diagnosis and treatment of the symptoms and sequelae of the disease. However, there is no cure.

Ivacaftor, a cystic fibrosis transmembrane CFTR potentiator, is indicated for the treatment of CF in patients ≥ 2 years of age who have one of the following mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, R117H, S1251N, S1255P, S549N, S549R, A455E, A1067T, D110E, D110H, D579G, D1152H, D1270N, E56K, E193K, F1052V, F1074L, G1069R, K1060T, L206W, P67L, R74W, R347H R352Q, R117C, R1070Q, R1070W, S945L, or S977F.1 In patients with unknown genotype, a Food and Drug Administration (FDA)-cleared CF mutation test should be used to detect the presence of the CFTR mutation followed by verification with bidirectional sequencing when recommended by the mutation test instructions for use. Ivacaftor has not shown to be effective in patients with CF who are homozygous for the F508del mutation in the CFTR.1

The CFTR protein is a chloride channel present at the surface of epithelial cells in multiple organs. Ivacaftor facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein.1 More than 1,800 disease-associated changes or mutations have been identified in the CFTR gene.2 According to the CF patient registry about 47% of patients have two copies of the F508del (Delta F508) mutation; more than 39% of patients with CF have one F508del mutation.

Ivacaftor – the active ingredient in Vertex’s Kalydeco® – is known as a CFTR potentiator, which helps keep the CFTR protein channels on the cell surface open longer to increase the flow of salt and water into and out of the cell.

Testing
Testing for CF is now part of the newborn screening (NBS) panel in all 50 states although protocols vary by state.3-5 A positive screening test does not indicate a diagnosis of CF; fewer than 10% of newborns with a positive CF test will actually be diagnosed with the disease.3 NBS for CF is a two-tiered process. The first is an analysis of immunoreactive trypsinogen (IRT). The second is a diagnostic test for CF (either a sweat chloride test ≥ 60 mmol/L or polymerase chain reaction [PCR] for gene mutations identifying two known CF mutations).

The analysis and interpretation of CF genotype information requires the use of appropriate testing techniques to identify CFTR mutation, standardized criteria for defining a CF-causing mutation, and an understanding of the contribution of the genetic background to the phenotypic variability of CF.6 Despite the potential usefulness of the information, acquiring a CF genotype can be difficult. Although currently available mutation screening panels can identify 90% of CFTR mutations (including G551D),
9.7% of genotyped individuals in the CF foundation patient registry have at least one unidentified mutation. Identification of CF mutations is more challenging in some populations; for example, the nature of distribution and frequency of CF-causing mutations in populations with Hispanic, African or Asian origins differs markedly from those identified in Caucasians. Several screening panels are available to detect CFTR mutations including a screening panels from Ambry® Genetics™. The tests have varying capacities for detecting mutations in CFTR and turn-around time varies by test ranging from 3 to 38 days.

FDA of Other Governmental Regulatory Approval

The FDA approved ivacaftor in January of 2012 for the treatment of a rare form of CF in patients ages 6 years and older who have the specific G551D mutation in the CFTR gene. The indication was later expanded in 2014 to include the G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, and S549R mutations in addition to the G551D mutation. In late 2014, the indication was once more expanded to patients that have a R117H mutation in the CFTR gene. In early 2015, the indication was again expanded to include those patients 2 years of age and older based on data extrapolated from efficacy in patients 6 years of age and older with support from population pharmacokinetic analyses showing similar drug exposure levels in adults and children 2 to less than 6 years of age. At the same time as the age expansion, a new formulation of ivacaftor was developed (oral granules in 50mg and 75mg unit-dose packets) for patients 2 to less than 6 years of age. The most recent FDA-indication expansion in May of 2017 included an additional 23 gene mutations (A455E, A1067T, D110E, D110H, D579G, D1152H, D1270N, E56K, E193K, F1052V, F1074L, G1069R, K1060T, L206W, P67L, R74W, R347H R352Q, R117C, R107OQ, R1070W, S945L, or S977F).

Rationale

Clinical Efficacy

G551D mutation in CFTR

The efficacy of ivacaftor in patients with CF and at least one G551D mutation in the CFTR gene was evaluated in two randomized, double-blind, placebo-controlled clinical trials in 213 clinically stable patients with CF (109 patients receiving ivacaftor 150 mg every 12 hours). One trial evaluated 161 patients with CF who were ≥ 12 years of age (mean age 26 years) with baseline forced expiratory volume in 1 second (FEV1) between 40% and 90% predicted (mean FEV1 64% predicted [range, 32% to 98%]). A second trial evaluated 52 patients who were 6 to 11 years of age (mean age 9 years) with baseline FEV1 between 40% and 105% predicted [mean FEV1 84% predicted [range, 44% to 134%]). Patients in both trials were continued on their prescribed CF therapies (e.g., TOBI® [tobramycin inhalation solution], Pulmozyme® [dornase alfa inhalation solution]) in addition to randomized treatment with the exception of hypertonic saline, which was not permitted.

In both studies, treatment with ivacaftor resulted in a significant improvement in FEV1. The treatment difference between ivacaftor and placebo for the mean absolute change in percent predicted FEV1 from baseline through Week 24 was +10.6% (P < 0.0001) in Trial 1 and +12.5 % (P < 0.0001) in Trial 2. These changes persisted through 48 weeks.

R117H-CFTR

KONDUCT was a Phase III, randomized, double-blind, placebo-controlled, parallel-group multicenter trial designed to evaluate the efficacy of ivacaftor in patients ≥ 6 years of age with the R117H-CFTR mutation (n = 69). Eligible patients were required to have at least one allele of the R117H-CFTR mutation and percent predicted FEV1 at screening of 40% to 90% (if ≥ 12 years of age) or 40% to 105% (if 6 to 11 years of age). Patients with any of the following CFTR gating mutations were excluded: G551D, G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D. Eligible patients were randomized 1:1 to treatment with ivacaftor at its FDA-approved dose or placebo.
for 24 weeks. The primary endpoint was the mean absolute change from baseline in percent predicted FEV1 through Week 24. At baseline the mean percent predicted FEV1 overall for the ivacaftor group was 75.7%.

The study did not meet its primary endpoint. The treatment difference for mean absolute change in percent predicted FEV1 through Week 24, using the full analysis set of 69 patients, was 2.1% and did not reach statistical significance. The treatment differences for the secondary endpoints: change from baseline in BMI at Week 24 (0.3 kg/m²) and the calculated hazard ratio (HR) for time-to-first pulmonary exacerbation (0.93) were both not statistically significant in the overall study population (n = 69). Statistically significant improvement in sweat chloride were observed in all subgroups.

FEV1 – Forced expiratory volume in 1 second; † Absolute change through Week 24; CI – Confidence interval.

Other mutations in CFTR
KONNECTION is an ongoing Phase III, randomized, double-blind, placebo-controlled, two-part crossover study evaluating the safety and efficacy of ivacaftor in patients ≥ 6 years of age with CF who have a non-G551D CFTR gating mutation on at least one allele and a FEV1 ≥ 40% predicted at screening (n = 39) [At least two patients with each of the included genotypes were enrolled]. In Part 1 of the study, patients were randomized to ivacaftor at its approved dose for 8 weeks or placebo for 8 weeks then switched to the opposite treatment for another 8 weeks. In Part 2 of the study, all patients received ivacaftor at its approved dose for 16 weeks (patient's initially randomized to placebo therefore received 24 weeks of continuous ivacaftor therapy. Eligible patients had the presence of one of the following CFTR mutation on at least one allele: G178R, s549N, G551S, G970R, G1244E, S1251N, S1255P, or G1349D. Patients were also required to have FEV1 ≥ 40% predicted. Patients with the G551D mutation were excluded from this study. The primary endpoint in Part 2 of the study was the absolute change from baseline in percent predicted FEV1 through 24 consecutive weeks of ivacaftor treatment. The full and safety sets included all patients randomized to treatment groups who received at least one dose of study drug. The absolute change from baseline in percent predicted FEV1 through 24 weeks of treatment for patients originally randomized to placebo was defined as the average of non-missing measurements after 2, 4, 8, 16, and 24 weeks of treatment. Mean patient age at baseline was 22.8 years and the mean percent predicted FEV1 was 78.4.

Results. All 36 patients who completed Part 1 entered Part 2 and completed the 16-week open-label extension study, 18 of whom are represented in the 24-week outcome measures. The mean absolute change from baseline in percent predicted FEV1 through Week 24 of ivacaftor treatment was 13.5% (range, -6.9, 36.5). The mean absolute change from baseline in BMI at Week 24 was 1.3 kg/m² (range, 0.16, 2.9); the mean absolute change from baseline in sweat chloride through Week 24 was -59.2 mmol/L (range, -93.5, 40.5); and the mean absolute change from baseline in CFQ-R respiratory domain score was 11.4 (range, -16.7, 33.3).

Homzygous for F508del Mutation in the CFTR Gene
Trial 3 was a 16-week, randomized, double-blind, placebo-controlled, parallel-group trial in 140 patients with CF age 12 years and older who were homozygous for the F508del mutation in the CFTR gene and who had FEV1 ≥40% predicted. Patients were randomized 4:1 to receive ivacaftor 150 mg (n=112) every 12 hours or placebo (n=28) in addition to their prescribed CF therapies. The mean age of patients enrolled was 23 years and the mean baseline FEV1 was 79% predicted (range 40% to 129%). As in Trials 1 and 2, patients who had persistent Burkholderia cenocepacia, Burkholderia dolosa, or Mycobacterium abscessus isolated from sputum at screening and those with abnormal liver function defined as 3 or more liver function tests (ALT, AST, AP, GGT, total bilirubin) ≥3 times the upper limit of normal were excluded. The use of inhaled hypertonic saline was not permitted.

The primary endpoint was improvement in lung function as determined by the mean absolute change from baseline through Week 16 in percent predicted FEV1. Treatment with ivacaftor resulted in no improvement in FEV1 relative to placebo in patients with CF homozygous for the F508del mutation in the CFTR gene [mean absolute change from baseline through Week 16 in percent predicted FEV1 was...
1.5% and -0.2% for patients in the ivacaftor and placebo-treated groups, respectively (P=0.15). There were no meaningful differences between patients treated with ivacaftor compared to placebo for secondary endpoints (change in CF symptoms, change in weight, or change in sweat chloride concentration.

**FDA-indications expanded (May 2017):**
Results from an in vitro cell-based model system have led to expanded FDA-indications for ivacaftor. Through in vitro lab experiments, cell lines were modified to produce mutant forms of CFTR proteins. CFTR-mediated chloride transport was measured in these cell lines before and after exposure to ivacaftor. A 10% net increase from baseline CFTR activity was set as a threshold expected to predict clinical benefit.


**References:**


Billing Coding/Physician Documentation Information

N/A Kalydeco® (ivacaftor) is specialty pharmacy benefit.

Additional Policy Key Words

81220 CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)

5.01.538 Policy #

Policy Implementation/Update Information

07/2012 New Policy Titled Kalydeco
07/2013 Reviewed policy – no changes made
07/2014 Reviewed policy – no changes made
07/2015 Reviewed policy – New FDA-approved indication added for R117H mutation; updated references; added Orkambi (FDA Approved July 2015)
07/2016 Reviewed policy – no changes made
02/2017 Updated expanded age indication for Orkambi
06/2017 Updated existing Kalydeco indications and separated Orkambi into a distinct Orkambi policy
08/2017 5 additional gene mutations added to expanded Kalydeco indications (2789+5G-A, 3272-26A-G, 3849+10kbC-T, 711+3A-G, E831X

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