ivacaftor (Kalydeco™)

Policy # 00327
Original Effective Date: 05/16/2012
Current Effective Date: 11/21/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on a review of available data, the Company may consider the use of ivacaftor (Kalydeco™)‡ for the treatment of cystic fibrosis (CF) to be **eligible for coverage**.**

Patient Selection Criteria:
Coverage eligibility will be considered for the use of ivacaftor (Kalydeco) when ALL of the following criteria are met:

- Patient is 12 months of age or older; AND
- Patient has a documented diagnosis of CF; AND
- Patient has confirmation of one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene as detected by an U.S. Food and Drug Administration (FDA)-cleared test: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, R117H, A455E, D1152H, F1074L, R74W, R1070W, D110H, E193K, L206W, R352Q, A1067T, D1270N, G1069R, R117C, S945L, D579G, F1052V, P67L, R1070Q, D110E, E56K, K1060T, R347H, S977F, 2789+5G→A, 3272-26A→G, 3849+10kb C→T, 711+3A→G, or E831X;* AND
- Patient is not homozygous for the *F508del* mutation in the CFTR gene.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of ivacaftor (Kalydeco) when patient selection criteria are not met to be **investigational.***

Background/Overview

CF is a serious genetic disorder affecting the lungs and other organs that ultimately leads to an early death. It is caused by mutations (defects) in a gene that encodes for a protein called CFTR that regulates ion (such as chloride) and water transport in the body. The defect in chloride and water transport results in the formation of thick mucus that builds up in the lungs, digestive tract and other parts of the body leading to severe respiratory and digestive problems, as well as other complications such as infections and diabetes.

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Kalydeco is a cystic CFTR potentiator, indicated for the treatment of CF in patients ≥ 12 months of age who have at least one of the following mutations in the CFTR gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, R117H, A455E, D1152H, F1074L, R74W, R1070W, D110H, E193K, L206W, R352Q, A1067T, D1270N, G1069R, R117C, S945L, D579G, F1052V, P67L, R1070Q, D110E, E56K, K1060T, R347H, S977F, 2789+5G→A, 3272-26A→G, 3849+10kb C→T, 711+3A→G, or E831X.* It is not effective in CF patients with two copies of the *F508* mutation in the CFTR gene, which is the most common mutation that results in CF. If a patient's mutation status is not known, an FDA-cleared CF mutation test should be used to determine whether a CFTR mutation is present. Kalydeco is supplied as a 150mg tablet to be taken twice daily for adults and children 6 years of age and older. In conjunction with the expanded age indication, there are unit dose oral granule packets of 50mg and 75mg for those ages 12 months to less than six years. Dosing of the oral granules is dependent on weight.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

The FDA approved ivacaftor (Kalydeco) 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 Kalydeco was developed (oral granules in 50mg and 75mg unit-dose packets) for patients 2 to less than 6 years of age. Then, in May of 2017, the following mutations in the CFTR gene were added to the FDA approved indication based on an in vitro cell-based model system: *A455E, D1152H, F1074L, R74W, R1070W, D110H, E193K, L206W, R352Q, A1067T, D1270N, G1069R, R117C, S945L, D579G, F1052V, P67L, R1070Q, D110E, E56K, K1060T, R347H, or S977F.* In August 2017, the following 5 mutations were added to the FDA approved indication based on clinical data: *2789+5G→A, 3272-26A→G, 3849+10kb C→T, 711+3A→G, E831X.* In August 2018, the label was updated to include patients 12 months of age or older.

Rationale/Source

Trials in Patients with CF who have a *G551D* Mutation in the CFTR Gene

Dose Ranging:

Dose ranging for the clinical program consisted primarily of one double-blind, placebo-controlled, cross-over trial in 39 adult (mean age 31 years) Caucasian patients with CF who had a forced expiratory volume in one second (FEV1) ≥ 40% predicted. Twenty patients with median predicted FEV1 at baseline of 56% (range: 42% to 109%) received Kalydeco 25, 75, 150mg or placebo every 12 hours for 14 days and 19 patients with median predicted FEV1 at baseline of 69% (range: 40% to 122%) received Kalydeco 150, 250mg or placebo every 12 hours for 28 days. The selection of the 150mg every 12 hours dose was primarily based

on nominal improvements in lung function (pre-dose FEV1) and changes in pharmacodynamic parameters (sweat chloride and nasal potential difference). The twice-daily dosing regimen was primarily based on an apparent terminal plasma half-life of approximately 12 hours. Selection of the 150mg dose of Kalydeco for children 6 to 11 years of age was based on achievement of comparable pharmacokinetics as those observed for adult patients.

Efficacy:
The efficacy of Kalydeco in patients with CF who have a *G551D* mutation in the CFTR gene was evaluated in 2 randomized, double-blind, placebo-controlled clinical trials in 213 clinically stable patients with CF (109 receiving Kalydeco 150mg twice daily). All eligible patients from these trials were rolled over into an open-label extension study.

Trial 1 evaluated 161 patients with CF who were 12 years of age or older (mean age 26 years) with baseline FEV1 between 40-90% predicted [mean FEV1 64% predicted (range: 32% to 98%)]. Trial 2 evaluated 52 patients who were 6 to 11 years of age (mean age 9 years) with baseline FEV1 between 40-105% predicted [mean FEV1 84% predicted (range: 44% to 134%)]. Patients who had persistent *Burkholderia cenocepacia, dolosa*, or *Mycobacterium abcessus* 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 (ULN) were excluded. Patients in both trials were randomized 1:1 to receive either 150mg of Kalydeco or placebo every 12 hours with food containing fat for 48 weeks in addition to their prescribed CF therapies (e.g., tobramycin, dornase alfa). The use of inhaled hypertonic saline was not permitted. The primary efficacy endpoint in both studies was improvement in lung function as determined by the mean absolute change from baseline in percent predicted pre-dose FEV1 through 24 weeks of treatment.

In both studies, treatment with Kalydeco resulted in a significant improvement in FEV1. The treatment difference between Kalydeco and placebo for the mean absolute change in percent predicted FEV1 from baseline through Week 24 was 10.6 percentage points ($P < 0.0001$) in Trial 1 and 12.5 percentage points ($P < 0.0001$) in Trial 2. These changes persisted through 48 weeks. Improvements in percent predicted FEV1 were observed regardless of age, disease severity, sex, and geographic region.

Other efficacy variables included absolute change in sweat chloride from baseline to week 24, time to first pulmonary exacerbation through week 48 (Trial 1 only), absolute change in weight from baseline to week 48, and improvement in CF symptoms including relevant respiratory symptoms such as cough, sputum production, and difficulty breathing. For the purpose of the study, a pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) as a result of 4 or more of 12 pre-specified sino-pulmonary signs/symptoms. Patients treated with Kalydeco demonstrated statistically significant improvements in risk of pulmonary exacerbations, CF symptoms (in Trial 1 only), and gain in body weight. Weight data, when expressed as body mass index (BMI) normalized for age and sex in patients < 20 years of age, was consistent with absolute change from baseline in weight.

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Trials in Patients with CF who have a *G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, or S549R* Mutation in the CFTR Gene
The efficacy and safety of Kalydeco in patients with CF who have a *G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N,* or *S549R* mutation in the CFTR gene were evaluated in a two-part, randomized, double-blind, placebo-controlled, crossover design clinical trial in 39 patients with CF. Patients who completed Part 1 of this trial continued into the 16-week open-label Part 2 of the study. The mutations studied were *G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P*, and *G1349D*. Patients were 6 years of age or older (mean age 23 years) with FEV1 ≥ 40% at screening [mean FEV1 at baseline 78% predicted (range: 43% to 119%)]. Patients with evidence of colonization with *Burkholderia cenocepacia, Burkholderia dolosa,* or *Mycobacterium abscessus* and those with abnormal liver function defined as 3 or more liver function tests (ALT, AST, AP, GGT, total bilirubin) ≥ 3 times the ULN at screening were excluded. Patients were randomized 1:1 to receive either 150mg of Kalydeco or placebo every 12 hours with food containing fat for 8 weeks in addition to their prescribed CF therapies during the first treatment period and crossed over to the other treatment for the second 8 weeks. The two 8-week treatment periods were separated by a 4- to 8-week washout period. The use of inhaled hypertonic saline was not permitted.

The primary efficacy endpoint was improvement in lung function as determined by the mean absolute change from baseline in percent predicted FEV1 through 8 weeks of treatment. Other efficacy variables included absolute change from baseline in sweat chloride through 8 weeks of treatment, absolute change from baseline in BMI at 8 weeks of treatment (including body weight at 8 weeks), and improvement in CF symptoms (including relevant respiratory symptoms such as cough, sputum production, and difficulty breathing) through 8 weeks of treatment. For the overall population of the 9 mutations studied, treatment with Kalydeco compared to placebo resulted in significant improvement in percent predicted FEV1 [10.7 through Week 8 ($P < 0.0001$)], BMI [0.66 kg/m^2 at Week 8 ($P < 0.0001$)], and CF respiratory symptom score [9.6 through Week 8 ($P = 0.0004$)]; however, there was a high degree of variability of efficacy responses among the 9 mutations. Based on clinical and pharmacodynamic (sweat chloride) responses to Kalydeco, efficacy in patients with the *G970R* mutation could not be established.

Trials in Patients with CF who have a *R117H* Mutation in the CFTR Gene
The efficacy and safety of Kalydeco in patients with CF who have an R117H mutation in the CFTR gene were evaluated in a randomized, double-blind, placebo-controlled, parallel-group clinical trial. This trial evaluated 69 clinically stable patients with CF who were 6 years of age or older (mean age 31 years). Patients who were 12 years and older had FEV1 at screening between 40-90% predicted, and patients who were 6-11 years of age had FEV1 at screening between 40-105% predicted. The overall mean FEV1 was 73% predicted at baseline (range: 33% to 106%). 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 ULN, were excluded. Patients were randomized 1:1 to receive either 150 mg of Kalydeco (n=34) or placebo (n=35) every 12 hours with food containing fat for 24 weeks in addition to their prescribed CF therapies.

The primary efficacy endpoint was improvement in lung function as determined by the mean absolute change from baseline in percent predicted FEV1 through 24 weeks of treatment. The treatment difference for absolute change in percent predicted FEV1 through Week 24 was 2.1 percentage points (analysis conducted with the full analysis set which included all 69 patients), and did not reach statistical significance. Other efficacy variables that were analyzed included absolute change in sweat chloride from baseline through Week 24, improvement in CF respiratory symptoms through Week 24 as assessed by the Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score, absolute change in BMI at Week 24, and time to first pulmonary exacerbation. The overall treatment difference for the absolute change from baseline in BMI at Week 24 was 0.3 kg/m2 and the calculated hazard ratio for time to first pulmonary exacerbation was 0.93, which were not statistically significant.

Other Mutations
Kalydeco was studied in patients that are homozygous for the *F508del* in the CFTR gene. The primary endpoint was improvement in lung function as determined by the mean absolute change from baseline through week 16 in percent predicted FEV1. The treatment difference did not reach a statistical significance, hence the lack of indication for those that are homozygous for the *F508del*.

The additional mutations *(A455E, D1152H, F1074L, R74W, R1070W, D110H, E193K, L206W, R352Q, A1067T, D1270N, G1069R, R117C, S945L, D579G, F1052V, P67L, R1070Q, D110E, E56K, K1060T, R347H, or S977F)* were not studied in clinical trials. The FDA based its decision for approval, in part, on the results of laboratory testing which it used in conjunction with evidence from earlier human clinical trials. A press release by the FDA stated, "Results from an in vitro cell-based model system have been shown to reasonably predict clinical response to Kalydeco. When additional mutations responded to Kalydeco in the laboratory test, researchers were thus able to extrapolate clinical benefit demonstrated in earlier clinical trials of other mutations. This resulted in the addition of gene mutations for which the drug is now indicated."

Study in patients heterozygous for *F508del* mutation
An additional study in patients heterozygous for the *F508del* mutation but with a second mutation predicted to be responsive to Kalydeco identified 5 additional mutations that were responsive and confirmed efficacy in 16 of the 28 mutations identified via *in vitro* testing only. This trial was conducted in 246 patients who were heterozygous for the *F508del* mutation and was a randomized, double-blind, placebo-controlled, 2-period, 3-treatment, 8-week crossover design trial. Patients were aged 12 years and older and had a percent predicted FEV_1 at screening between 40 and 90. Patients with evidence of colonization with organisms associated with a more rapid decline in pulmonary status (e.g., *Burkholderia cenocepacia, Burkholderia dolosa,* or *Mycobacterium abscessus*) and those with abnormal liver function at screening were excluded.

The primary efficacy endpoint was the mean absolute change from study baseline in percent predicted FEV_1 averaged at Weeks 4 and 8 of treatment. For the overall population, treatment with Kalydeco resulted in statistically significant improvement in FEV_1 compared to placebo (4.7 percentage points from baseline to average of week 4 and week 8). Additional mutations identified were *2789+5G→A, 3272-26A→G, 3849+10kb C→T, 711+3A→G,* and *E831X*.

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References

1. Kalydeco tablets (ivacaftor) [package insert] Vertex Pharmaceuticals, Inc., Cambridge, MA: December 2017.
2. FDA News Release. FDA approves Kalydeco to treat rare form of cystic fibrosis. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm289633.htm
3. FDA News Release: FDA expands approved use of Kalydeco to treat additional mutations of cystic fibrosis. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm559212.htm
4. News Release: FDA Approves Kalydeco (ivacaftor) for more than 600 people ages 2 and older with cystic fibrosis who have certain residual function mutations. http://investors.vrtx.com/releasedetail.cfm?releaseid=1035299

Policy History

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05/03/2012	Medical Policy Committee review
05/16/2012	Medical Policy Implementation Committee approval. New policy.
05/02/2013	Medical Policy Committee review
05/22/2013	Medical Policy Implementation Committee approval. Revised the Patient Selection Criteria coverage statement, the second bullet of the criteria and the investigational statement for clarity and to be consistent with the Pharmacy call tree. No change to coverage eligibility.
05/01/2014	Medical Policy Committee review
05/21/2014	Medical Policy Implementation Committee approval. Expanded the list of mutations of the CFTR gene to match the package insert. Modified background info and FDA info to reflect additional gene mutations. Also added clinical trial info for the additional gene mutations.
02/05/2015	Medical Policy Committee review
02/18/2015	Medical Policy Implementation Committee approval. Added the newest gene mutation (R117H) that allows for treatment with Kalydeco.
05/07/2015	Medical Policy Committee review
05/20/2015	Medical Policy Implementation Committee approval. Updated policy to reflect FDA expanded indications for patients ages 2-6yrs.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
05/05/2016	Medical Policy Committee review
05/18/2016	Medical Policy Implementation Committee approval. No change to coverage eligibility.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
07/06/2017	Medical Policy Committee review
07/19/2017	Medical Policy Implementation Committee approval. Added new mutations (*A455E, D1152H, F1074L, R74W, R1070W, D110H, E193K, L206W, R352Q, A1067T, D1270N, G1069R, R117C, S945L, D579G, F1052V, P67L, R1070Q, D110E, E56K, K1060T, R347H, or S977F)* to the policy.
02/01/2018	Medical Policy Committee review
02/21/2018	Medical Policy Implementation Committee approval. Added new mutations (*2789+5G→A, 3272-26A→G, 3849+10kb C→T, 711+3A→G,* and *E831X)* to the policy.
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. Updated age requirement to state that patients 12 months of age and older are eligible for Kalydeco.

Next Scheduled Review Date: 11/2019

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Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J3490, J8499
ICD-10 Diagnosis	E84.0-E84.9

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.