PREMERA | BLUE CROSS

PHARMACY POLICY – 5.01.539

Kalydeco® (ivacaftor), Orkambi® (lumacaftor / ivacaftor), and Symdeko™ (tezacaftor / ivacaftor)

Effective Date:	Nov. 1, 2018	RELATED MEDICAL POLICIES:
Last Revised:	Oct. 26, 2018	None
Replaces:	N/A	

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Cystic fibrosis is a condition that causes thick, sticky mucus to build up in the lungs, digestive tract, and other areas of the body and is caused by change(s) to the CFTR gene. A child inherits one CFTR gene from each parent. If two faulty CFTR genes are inherited, it leads to cystic fibrosis. (If children inherit one problematic CFTR gene, they usually won't have symptoms of cystic fibrosis but can pass the changed gene to their children.) The change(s) in the CFTR gene results in problems with how salt moves in and out of cells. The end result is a buildup of sticky, thick mucus. Drugs have been developed that target specific changes on the CFTR gene. This policy describes when these drugs may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

<table>
<tr><th>Drug</th><th>Medical Necessity</th></tr>
<tr><td>Kalydeco® (ivacaftor)</td><td>
Kalydeco® (ivacaftor) may be considered medically necessary for the treatment of cystic fibrosis (CF) in patients age 1 years and older who have any of the following mutations in the CFTR gene or any mutation subsequently added to the FDA-approved indication:
<table>
<tr><th colspan="6">CFTR Gene Mutations Responsive to Kalydeco®</th></tr>
<tr><td>2789+5G→A</td><td>D110H</td><td>F1052V</td><td>G551S</td><td>R117H</td><td>S549R</td></tr>
<tr><td>3272-26A→G</td><td>D1152H</td><td>F1074L</td><td>K1060T</td><td>R347H</td><td>S945L</td></tr>
<tr><td>3849+10kbC→T</td><td>D1270N</td><td>G1069R</td><td>L206W</td><td>R352Q</td><td>S977F</td></tr>
<tr><td>711+3A→G</td><td>D579G</td><td>G1244E</td><td>P67L</td><td>R74W</td><td></td></tr>
<tr><td>A1067T</td><td>E193K</td><td>G1349D</td><td>R1070Q</td><td>S1251N</td><td></td></tr>
<tr><td>A455E</td><td>E56K</td><td>G178R</td><td>R1070W</td><td>S1255P</td><td></td></tr>
<tr><td>D110E</td><td>E831X</td><td>G551D</td><td>R117C</td><td>S549N</td><td></td></tr>
</table>
Documentation of at least one copy of one of the above mutations is required for Kalydeco® (ivacaftor) coverage.
An FDA-cleared CF mutation test should be performed prior to prescribing Kalydeco® to detect the presence of the mutation to validate presence one of the above listed genes.

Note: Since CFTR is recessive, heterozygous patients with one allele containing one of the above mutations are candidates for therapy; however, a minority of CF patients carry these mutations. There is no demonstrated benefit in others, nor is any expected.

Kalydeco® (ivacaftor) is considered not medically necessary when used in patients that have homozygous F508del, and in patients that have G970R and do not have at least one copy of one of the above target mutations.

Kalydeco® (ivacaftor) is considered investigational when used in patients that do not meet any of the above criteria.
</td></tr>
<tr><td>Orkambi® (lumacaftor/ivacaftor)</td><td>Orkambi® (lumacaftor/ivacaftor) may be considered medically necessary for the treatment of cystic fibrosis (CF) in patients age 2 years and older who are homozygous for the F508del mutation in the CFTR gene. If the patient's</td></tr>
</table>

<table>
<tr><th>Drug</th><th>Medical Necessity</th></tr>
<tr><td></td><td>genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene. Orkambi may also be considered medically necessary for any mutation subsequently added to the FDA-approved indication.

Orkambi® (lumacaftor/ivacaftor) is considered investigational when used in patients that do not meet any of the above criteria.</td></tr>
<tr><td>Symdeko™ (tezacaftor/ivacaftor)</td><td>Symdeko™ (tezacaftor/ivacaftor) may be considered medically necessary for the treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the F508del mutation in the CFTR gene or heterozygous for F508del with a residual function mutation. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the F508del mutation on at least one allele of the CFTR gene.

Symdeko™ (tezacaftor/ivacaftor) may also be considered medically necessary for any mutation subsequently added to the FDA-approved indication. Currently known responsive mutations are listed in the table below:
<table>
<tr><th colspan="6">CFTR Gene Mutations Responsive to Symdeko™</th></tr>
<tr><td>2789+5G→A</td><td>A455E</td><td>D579G</td><td>F1074L</td><td>R1070W</td><td>R74W</td></tr>
<tr><td>3272-26A→G</td><td>D110E</td><td>E193K</td><td>F508Δ</td><td>R117C</td><td>S945L</td></tr>
<tr><td>3849+10kbC→T</td><td>D110H</td><td>E56K</td><td>K1060T</td><td>R117H</td><td>S977F</td></tr>
<tr><td>711+3A→G</td><td>D1152H</td><td>E831X</td><td>L206W</td><td>R347H</td><td></td></tr>
<tr><td>A1067T</td><td>D1270N</td><td>F1052V</td><td>P67L</td><td>R352Q</td><td></td></tr>
</table>
Symdeko™ (tezacaftor/ivacaftor) is considered investigational when used in patients that do not meet any of the above criteria.</td></tr>
</table>

Length of Approval	
Approval	**Criteria**
Initial Approval	Initial approval for 6 months requires both of the following:

Length of Approval	
Approval	**Criteria**
	• Genetically confirmed diagnosis of CF with the one of the above genotypes **AND** • The patient does not have liver function tests (LFT) above 3X upper limit of normal (ULN)
Reauthorization	**Continued therapy will be approved for periods of one year as long as the above conditions are met, and the patient has shown and continues to show improvement in FEV1, symptoms or stabilization of disease.** **Reauthorization may be approved for up to one year.**

Coding

N/A

Related Information

Benefit Application

This policy is managed through the Pharmacy benefit.

Evidence Review

Description

Cystic Fibrosis

Cystic fibrosis is an autosomal recessive genetic disorder passed down through families that causes thick, sticky mucus to build up in the lungs, digestive tract, and other areas of the body. 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.

CF is caused by a mutation in the gene cystic fibrosis transmembrane conductance regulator (CFTR). The most common mutation, ΔF508, is a deletion (Δ) of three nucleotides that results in a loss of the amino acid phenylalanine (F) at the 508th position on the protein. This mutation accounts for two-thirds (66-70%) of CF cases worldwide and 90% of cases in the United States; however, there are over 1500 other mutations that can produce cystic fibrosis. Although most people have two working copies (alleles) of the CFTR gene, only one is needed to prevent cystic fibrosis. CF develops when neither allele can produce a functional CFTR protein. Thus, CF is considered an autosomal recessive disease.

Cystic fibrosis 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, and CF affects all ethnic and racial groups, although is most common in Caucasians. There is no cure for cystic fibrosis, and despite progress in the treatment of the disease, the predicted median age of survival for a person with CF is the mid-30's. In the United States, approximately 90% of patients carry at least one ΔF508 allele with 60-70% of patients being homozygous for ΔF508. Worldwide, ~4% of patients carry the G551D mutation. Most of these are heterozygous, with the other allele having ΔF508. Since CF is a recessive trait, these individuals would be expected to respond to treatment with ivacaftor.

The CFTR gene encodes an epithelial chloride channel, the CFTR protein, which is responsible for aiding in the regulation of salt and water absorption and secretion in multiple organ systems, including the lungs, pancreas, intestinal tract, biliary tract, sweat gland, and reproductive tract. Mutations in the CFTR gene that result in CF disease do so by reducing the quantity of CFTR protein channels that reach the cell surface or by reducing the chloride transport function of CFTR protein channels at the cell surface. CFTR protein channel dysfunction is the underlying cause of CF disease.

The failure to regulate chloride transport in these organs results in the multisystem pathology associated with CF. The majority of patients with CF die from progressive lung disease. In the

airways of patients with CF, impaired chloride channel function results in a reduction of the height of the periciliary fluid layer. This occurs as a consequence of altered osmotic forces secondary to reduced CFTR-dependent chloride ion secretion and its associated sodium ion hyperabsorption into the epithelia. The reduced height of the periciliary fluid layer results in a reduced ability of the cilia to effectively clear mucus, trapped pathogens and particulates from the lungs. Mucus retention then leads to airway plugging, chronic infection of the lung passages, and inflammatory responses that in turn cause scarring of airway tissue and progressive and permanent loss of lung function.

While the clinical manifestations of CF vary between individuals, several studies indicate an association between the type of CFTR mutations present in an individual, the degree of residual CFTR protein function and the severity of CF pulmonary disease, pancreatic function, and mortality. Severe CF disease ("classical CF") is typically characterized by an early onset of clinical manifestations, a high incidence of pancreatic insufficiency, airway colonization with Pseudomonas aeruginosa, a more rapid rate of lung function decline, and shorter life expectancy. Most patients with severe CF carry 2 CFTR mutations associated with minimal CFTR protein function and therefore sweat chloride concentrations in individuals with severe disease are generally 90 mmol/L or greater. Most of the common CFTR mutations are associated with minimal CFTR protein channel function and therefore with a severe CF disease course. While reports of individual cases and small cohorts of patients show variable phenotypes in patients carrying the G551D mutation, the 3 largest genotype phenotype association studies that evaluated patients from different geographical regions have classified the G551D mutation as being associated with severe CF disease, with rates of lung disease progression and mortality that are similar to other severe phenotypes.

The F508del mutation is the most common mutation in the CFTR gene associated with CF disease. It causes a defect in CFTR protein folding. F508del-CFTR proteins are generally retained and degraded within the cell instead of being trafficked to the apical cell membrane. The result is little to no CFTR protein reaching the cell surface and as a consequence severe reduction in CFTR-mediated chloride ion transport.

In contrast to mutations such as F508del, the G551D mutation in the CFTR gene does not impact the quantity of CFTR channels present at the cell membrane. The G551D mutation is an amino acid substitution located in the first of two nucleotide binding domains within the CFTR protein. The nucleotide binding domains bind and hydrolyze ATP to drive opening (or gating) of the CFTR channel pore, thereby allowing transport of chloride and other ions. The G551D substitution affects the ATP binding ability of the nucleotide binding domain, thereby greatly reducing channel gating activity and, as a consequence, CFTR-mediated chloride ion transport. G551D is the most prevalent CFTR gating mutation. Mutations in the CFTR gene that result in

alterations of the CFTR channel pore structure can also limit or eliminate the rate of ion flow through the channel. Mutations of this type are referred to as "conductance" mutations.

There are societal, humanistic and economic burdens associated with cystic fibrosis.

- Patients with CF experience severe progressive dysfunction primarily in the lungs and digestive system, resulting in life-threatening manifestations that persist over their lifetime and negatively impact quality of life.
- Rates of depression among CF patients and their caregivers have consistently been shown to be higher than the general population.
- Maintenance therapy for CF places a significant burden on patients with CF as well as caregivers
- The number of outpatient visits to health care providers is high, with adults averaging 12 doctor visits and children averaging 10 visits annually in a study of a large commercial/ Medicaid U.S. health insurer.
- Comorbidities and manifestations of the disease increase treatment burden.

Kalydeco® (ivacaftor)

Kalydeco® (ivacaftor) is a potentiator of the CFTR protein, and is the first drug that directly targets the defective CFTR protein rather than cystic fibrosis symptoms. The CFTR protein is a chloride channel present at the surface of epithelial cells in multiple organs. Ivacaftor appears to increase the probability of CFTR channel opening (or gating) to enhance chloride transport, which allows chloride and bicarbonate flow across epithelial cell membranes present in patients with the G551D mutation Different testing panels might be employed for identification of CFTR mutations in patients diagnosed with CF, in relatives of CF patients, or in newborn screening. The minimum standard panel includes G551D and therefore would identify suitable candidates for ivacaftor therapy. Sensitivity for detection of G551D in generalized screening is 88%; specificity is greater than 99%.

Ivacaftor is the only drug currently available to treat the underlying defect identified in a subpopulation of patients with cystic fibrosis, namely those with at least one copy of the G551D-CFTR mutation. There are currently no other drugs available to treat the underlying cause of CF, but there are a number of compounds available that are used to treat the symptoms and the sequelae of the disease. Early diagnosis, improved and more consistent patient management, the advent of new pharmacological agents and advances in non-pharmacology approaches

have led to improvement in the survival of CF patients. Ivacaftor was approved the United States FDA in January 2012 and it is not currently included in treatment guidelines.

Efficacy/Effectiveness

Efficacy of ivacaftor was demonstrated in cystic fibrosis patients with a G551D mutation in two randomized, double-blind, placebo controlled Phase 3 clinical trials of 48 weeks duration. Treatment with ivacaftor demonstrated improved lung function (absolute change in percent predicted FEV1 from baseline to week 24) by 10 and 12% in trials in adolescents/adults, and in children 6 to 11 years of age, respectively. Secondary endpoints, including weight gain and time to first pulmonary exacerbation, also support efficacy. No evidence of real world comparative effectiveness was available at the time of review. Ivacaftor is a first in class drug for which there is no approved CF therapy that could serve as an active comparator.

In 2014 the FDA approved ivacaftor for several other CFTR mutations: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N and S549R. The efficacy of ivacaftor in patients with these polymorphisms was evaluated in a two-part double-blind placebo-controlled crossover RCT with 39 patients ≥6 years old (mean age 23) with baseline FEV1 ≥40% of predicted (mean 78%, range: 43% to 119%). Patients received either 150 mg of ivacaftor or placebo every 12 hours for 8 weeks in addition to their routine meds. After a 4-8 week washout period they were crossed over to the other treatment for the second 8 weeks. Treatment with ivacaftor significantly improved percent predicted FEV1 (10.7% through Week 8, $P < 0.0001$). Improvements from baseline in sweat chloride and BMI, and improvement in CF symptoms (including cough, sputum production, and difficulty breathing) were also observed; however, there was a high degree of variability of efficacy responses among the 9 mutations. Based on clinical and pharmacodynamic (sweat chloride) responses to ivacaftor, efficacy in patients with the G970R mutation could not be established.

The deletion mutation at F508 in the CFTR gene is the most common in the U.S. population; however, a 16-week trial of ivacaftor in patients with homozygous F508del failed to produce significant improvement.

Safety/Tolerability

Ivacaftor was well-tolerated, and demonstrated no major safety signals in clinical trials. No deaths were reported, AEs were generally those associated with cystic fibrosis (i.e. GI issues, exacerbations, pneumonia). Common adverse events included headache, upper respiratory tract

infection, nasal congestion, nausea, rash, rhinitis, dizziness, arthralgia, and bacteria in sputum, generally well-tolerated. Laboratory assessments suggest the possibility that ivacaftor may be associated with an increase in liver transaminases, but the increase was only slightly over those who received placebo treatment in the clinical trials. Transaminases are recommended to be monitored in patients receiving the drug.

Orkambi® (lumacaftor/ivacaftor)

Orkambi® (lumacaftor/ivacaftor) is a combination of two drugs: a CFTR potentiator (ivacaftor) and a drug to increase the quantity of CFTR ion channels (lumacaftor). Together they provide a new approach to the treatment of cystic fibrosis in patients homozygous for the F508del CFTR mutation by improving the quantity and function of the CFTR protein.

Efficacy/Effectiveness

Lumacaftor/Ivacaftor displayed a modest improvement in patients homozygous for the F508del CFTR mutation in measureable outcomes of lung function, BMI, quality of life and decreased pulmonary exacerbations in the two phase III trials (total n=1108), TRAFFIC and TRANSPORT. ppFEV1 increased +2.8%, BMI P&T Committee Agenda 126 September 2015 Vol. 16, No. 3 increased +0.24, CFQR-RD score increased +2.2 and the rate ratio of pulmonary exacerbations was 0.61 when compared to placebo. Results were based off of 24 week trials in patients 6 years and older. The clinical significance in the absolute change in FEV1 as well as the change in the other outcomes is unknown.

Safety/Tolerability

Lumacaftor/Ivacaftor displayed a safety profile similar to placebo in most adverse event types, with the primary exception in serious adverse events where LUM/IVA exhibited superior safety (rate of SAE 28.6% inplacebo vs 17.3% in LUM/IVA). This was primarily a result of significantly decreased pulmonaryexacerbations of CF, 24.1% placebo vs. 11.1% LUM/IVA.

Symdeko™ (tezacaftor / ivacaftor)[22]

Symdeko™ (tezacaftor / ivacaftor) is a combination CFTR corrector and potentiator indicated for patients with CF and are homozygous for the F508del mutation, or heterozygous for F508del and a residual function mutation. Tezacaftor/ivacaftor provides a novel treatment option for patients heterozygous for F508del and a residual mutation function while providing an alternative to Orkambi® for those homozygous for F508del.

Efficacy/Effectiveness[22,23]

Symdeko™ (tezacaftor/ivacaftor) was evaluated in two pivotal clinical trials assessing efficacy in patients homozygous for the Phe508del mutation or heterozygous for Phe508del and a residual function mutation. These trials showed modest improvements in lung function and patient-centered quality of life measures.

EVOLVE was a phase III, double-blind, multicenter, placebo-controlled, parallel group RCT that randomized 510 patients older than 12 years and homozygous for the Phe508del CFTR mutation and FEV1 between 40% and 90% to tezacaftor/ivacaftor or placebo. The primary endpoint of absolute change in predicted FEV1 through week 24 was 3.4% (2.7%, 4.0%) and -0.6% (-1.3%, 0.0%) and a difference of 4.0% (3.1%, 4.8%; $p<0.001$) for TEZ/IVA and placebo respectively. There was also improvement in relative change from predicted FEV1 with a difference of 6.8% (5.3%, 8.3%; $p<0.001$) from tezacaftor/ivacaftor over placebo. Quality of life measures related to lung function was also improved in the tezacaftor/ivacaftor group, with an improvement of 5.0 (3.5, 6.5) points in the CFQ-R respiratory domain score and a difference of 5.1 (3.2, 7.0) points over placebo. The EVOLVE trial is of good quality and demonstrates superiority of tezacaftor/ivacaftor over placebo. However, the standard of care for patients with a homozygous Phe508del mutation is currently Orkambi® (lumacaftor/ivacaftor) and an active comparator would have been more appropriate and clinically relevant for decision-making.

EXPAND was a phase III, double-blind, placebo-controlled, crossover RCT that evaluated 244 patients 12 years or older who are heterozygous for the Phe508del CFTR mutation and a second allele with a residual-function CFTR mutation. Absolute change in predicted FEV1 was 4.7% (3.7%, 5.8%; $p<0.001$) for IVA vs PBO, 6.8% (4.7%, 7.8%; $p<0.001$) for tezacaftor/ivacaftor vs PBO, and 2.1% (1.2%, 2.9%; $p<0.001$) for tezacaftor/ivacaftor vs IVA. Tezacaftor/ivacaftor also increased CFQ-R scores by 11.1 (8.7, 13.6; $p<0.001$) versus PBO. The crossover design of EXPAND is not optimal due to confounding by carryover effects, although the 8 week washout period is comparable to the treatment period of 8 weeks. The difficulty of obtaining patients

with rare mutations to power the study for a traditional parallel group design should also be noted.

Safety/Tolerability[22-24]

Tezacaftor/ivacaftor was well-tolerated in clinical trials and comparable to placebo or IVA alone. No patients died in any clinical trials due to drug treatment and discontinuation rates were low. Overall, tezacaftor/ivacaftor did not show signals for major adverse events due to drug treatment alone and can be evaluated as safe within the clinical trial duration of 24 months.

EVOLVE evaluated 509 patients for safety with 90.4% patients in the tezacaftor/ivacaftor group and 95.0% in the placebo group reporting at least one adverse event. Most events were of mild severity (41.8%) or moderate severity (40.9%). Safety signals were consistent across all subgroups for tezacaftor/ivacaftor. Serious safety events were reported in 31 patients (12.4%) in the tezacaftor/ivacaftor group and in 47 (18.2%) in the placebo group. 7 patients in the tezacaftor/ivacaftor and 8 patients in the placebo group discontinued the trial due to AEs. Only one patient in the placebo arm had coincident elevations in liver function tests (LFTs) 3x the upper limit of normal (ULN). Overall, the incidence of adverse events associated with elevated LFTs was low, occurring in 10 patients (4.0%) in the tezacaftor/ivacaftor group and 15 (5.8%) in the placebo group. Common side effects (>10%) were infective pulmonary exacerbation, cough, headache, nasopharyngitis, and increased sputum production which are consistent with CF symptoms.

EXPAND had similar safety signals to EVOLVE with the majority of patients having adverse events that were considered either mild or moderate in severity. Four patients (2%) in the tezacaftor/ivacaftor group, eight (5%) in the IVA group, and nine (6%) in the placebo group had severe or life-threatening adverse events. The most common events were cough, infective pulmonary exacerbation of CF, headaches and hemoptysis. Adverse events that were associated with respiratory symptoms were less common in the tezacaftor/ivacaftor group than in the placebo group. No report of bronchoconstriction or acute reduction in FEV1 within 4 hours of treatment was noted.

Donaldson et al was a phase 2, placebo-controlled, double-blind, multicenter, RCT comparing tezacaftor/ivacaftor, TEZ and placebo in patients homozygous for F508del mutation or compound heterozygous for F508del and G551D. 152 patients homozygous for F508del (88.4%) had at least 1 adverse event, with an incidence of 30 (90.9%) patients in the TEZ arm, 92 (86.8%) patients in the tezacaftor/ivacaftor arm, and 30 (90.9%) patients in the placebo arm. The majority (81.4%) of adverse events were mild to moderate in nature. The most common adverse events

by subject were infective pulmonary exacerbation of CF, cough, increased sputum, nausea, diarrhea, headache, and fatigue.

2013 Update

Search of recent literature found no new information that would modify this policy.

2014 Update

Added new CFTR mutations that now have evidence of ivacaftor efficacy and have been added to the labeled indication.

2015 Update

Added new combination product, Orkambi, approved by the FDA in 2015. A literature search from 7/1/14 through

10/31/15 did not find any other new evidence that would indicate need to change the policy criteria.

2016 Update

Orkambi®'s age criteira has changed from 12 to 6 years of age and older.

The age stated in this policy for which Kalydeco® (ivacaftor) is considered medically necessary for the treatment of cystic fibrosis is age 6 and above. This age is based on the FDA labeling. The age stated in this policy for which Orkambi® (lumacaftor/ivacaftor) is considered medically necessary for the treatment of cystic fibrosis is age 6 years and older which is based on the FDA labeling.

2017 Update

Updated Kalydeco®'s age criteria from 6 years of age and older to 2 years of age and older. The age stated in this policy for which Kalydeco® (ivacaftor) is considered medically necessary for the treatment of cystic fibrosis is age 2 and above, which is based on the revised FDA labeling.

Verification with bi-directional sequencing when recommended by the mutation test instructions for use is added to follow the CF mutation test.

2018 Update

Added Symdeko™ (tezacaftor/ivacaftor) as a treatment option along with evidence for safety and tolerability. The age listed in the Symdeko™ policy statement is based on FDA labeling. Updated Orkambi age to 2 years. Updated Kalydeko age to one year, per label changes. Added table of target mutations for Symdeko.

References

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History

Date	Comments
06/12/12	New policy, add to Prescription Drug section.

Date	Comments
07/08/13	Minor Update – Clarification was added to the policy that it is managed through the member's pharmacy benefit; this is now listed in the header and within the coding section.
10/14/13	Replace policy. Policy updated with literature review; no change to policy statement.
12/08/14	Annual Review. Policy updated with additional gene mutations within the medically necessary policy statement; a not medically necessary policy statement is added addressing specific patient pools, with clarification added that all other uses of ivacaftor are investigational when policy criteria are not met. Reference 7 removed (duplicate of #2); reference 10 added.
01/13/15	Annual Review. Medically necessary policy statement updated with the addition gene mutation R117H, recently approved by the FDA; additional language added to include "any mutation subsequently added to the FDA-approved indication".
12/08/15	Interim Review. Policy updated with literature review. Policy title expanded to match the scope of policy which now includes Lumacaftor/Ivacaftor (Orkambi). Medically necessary policy statement added to address Orkambi to treat CF in patients 12 and older when criteria are met.
02/09/16	Annual Review. Medically necessary policy statement for ivacaftor now includes documentation of at least on copy of the listed mutations; CF mutation testing required if genotype is unknown.
12/01/16	Interim Review, approved November 8, 2016. Orkambi®'s age criteira has changed from 12 to 6 years of age and older. Information added to explain the application of age for this policy is based on FDA-labelled indication.
10/01/17	Annual Review, approved September 12, 2017. Kalydeco®'s age criteria has changed from 6 to 2 years of age and older. The age stated in this policy for which Kalydeco® (ivacaftor) is considered medically necessary for the treatment of cystic fibrosis is age 2 and above, which is based on the FDA labeling. Verification with bi-directional sequencing when recommended by the mutation test instructions for use is added to follow the CF mutation test.
03/01/18	Interim Review, approved February 13, 2018. Added Symdeko™ (tezacaftor/ivacaftor) as a treatment option along with evidence for safety and tolerability. References 23, 24, and 25 added. Title updated from "Kalydeco® (ivacaftor) and Orkambi® (lumacaftor / ivacaftor) " to "Kalydeco® (ivacaftor) ,Orkambi® (lumacaftor / ivacaftor), and Symdeko™ (tezacaftor / ivacaftor)"
06/01/18	Interim Review, approved May 3, 2018. Removed criteria requiring sputum cultures free of Burkholderia cenocepacia, dolosa, or Mycobacterium abcessus.
09/01/18	Minor update. Under the 2018 update, added a statement that the age for Symdeko™ is based on FDA labeling.

Date	Comments
11/01/18	Annual Review, approved October 26, 2018. Orkambi age updated. Kalydeco age updated. Added table of updated target mutations for Symdeko.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

PREMERA | BLUE CROSS

An Independent Licensee of the Blue Cross Blue Shield Association

Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:

- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html.

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

አማሪኛ (Amharic):
ይህ ማስታወቂያ አስፈላጊ መረጃ ይዟል። ይህ ማስታወቂያ ስለ ማመልከቻዎ ወይም የ Premera Blue Cross ሽፋን አስፈላጊ መረጃ ሊኖረው ይችላል። በዚህ ማስታወቂያ ውስጥ ቁልፍ ቀኖች ሊኖሩ ይችላሉ። የጤናን ሽፋንዎን ለመጠበቅና በእከፋፈል እርዳታ ለማግኘት በተውሰኑ የጊዜ ገደቦች እርምጃ መውሰድ ይገባዎት ይሆናል። ይህን መረጃ እንዲያገኙ እና ያለምንም ክፍያ በቋንቋዎ እርዳታ እንዲያገኙ መብት አለዎት።በስልክ ቁጥር 800-722-1471 (TTY: 800-842-5357) ይደውሉ።

العربية (Arabic):
يحوي هذا الإشعار معلومات هامة. قد يحوي هذا الإشعار معلومات مهمة بخصوص طلبك أو التغطية التي تريد الحصول عليها من خلال Premera Blue Cross. قد تكون هناك تواريخ مهمة في هذا الإشعار. وقد تحتاج لاتخاذ إجراء في تواريخ معينة للحفاظ على تغطيتك الصحية أو للمساعدة في دفع التكاليف. يحق لك الحصول على هذه المعلومات والمساعدة بلغتك دون تكبد أية تكلفة. اتصل بـ800-722-1471 (TTY: 800-842-5357)

中文 (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知內可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357)。

Oromoo (Cushite):
Beeksisni kun odeeffannoo barbaachisaa qaba. Beeksisti kun sagantaa yookan karaa Premera Blue Cross tiin tajaajila keessan ilaalchisee odeeffannoo barbaachisaa qabaachuu danda'a. Guyyaawwan murteessaa ta'an beeksisa kana keessatti ilaalaa. Tarii kaffaltiidhaan deeggaramuuf yookan tajaajila fayyaa keessaniif guyyaa dhumaa irratti wanti raawwattan jiraachuu danda'a. Kaffaltii irraa bilisa haala ta'een afaan keessaniin odeeffannoo argachuu fi deeggarsa argachuuf mirga ni qabaattu. Lakkoofsa bilbilaa 800-722-1471 (TTY: 800-842-5357) tii bilbilaa.

Français (French):
Cet avis a d'importantes informations. Cet avis peut avoir d'importantes informations sur votre demande ou la couverture par l'intermédiaire de Premera Blue Cross. Le présent avis peut contenir des dates clés. Vous devrez peut-être prendre des mesures par certains délais pour maintenir votre couverture de santé ou d'aide avec les coûts. Vous avez le droit d'obtenir cette information et de l'aide dans votre langue à aucun coût. Appelez le 800-722-1471 (TTY: 800-842-5357).

Kreyòl ayisyen (Creole):
Avi sila a gen Enfòmasyon Enpòtan ladann. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kèk aksyon avan sèten dat limit pou ka kenbe kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resevwa enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rele nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):
Diese Benachrichtigung enthält wichtige Informationen. Diese Benachrichtigung enthält unter Umständen wichtige Informationen bezüglich Ihres Antrags auf Krankenversicherungsschutz durch Premera Blue Cross. Suchen Sie nach eventuellen wichtigen Terminen in dieser Benachrichtigung. Sie könnten bis zu bestimmten Stichtagen handeln müssen, um Ihren Krankenversicherungsschutz oder Hilfe mit den Kosten zu behalten. Sie haben das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Rufen Sie an unter 800-722-1471 (TTY: 800-842-5357).

Hmoob (Hmong):
Tsab ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb. Tej zaum tsab ntawv tshaj xo no muaj cov ntsiab lus tseem ceeb txog koj daim ntawv thov kev pab los yog koj qhov kev pab cuam los ntawm Premera Blue Cross. Tej zaum muaj cov hnub tseem ceeb uas sau rau hauv daim ntawv no. Tej zaum koj kuj yuav tau ua qee yam uas peb kom koj ua tsis pub dhau cov caij nyoog uas teev tseg rau hauv daim ntawv no mas koj thiaj yuav tau txais kev pab cuam kho mob los yog kev pab them tej nqi kho mob ntawd. Koj muaj cai kom lawv muab cov ntshiab lus no uas tau muab sau ua koj hom lus pub dawb rau koj. Hu rau 800-722-1471 (TTY: 800-842-5357).

Iloko (Ilocano):
Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalin nga adda ket naglaon iti napateg nga impormasion maipanggep iti apliksayonyo wenno coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a petsa iti daytoy a pakdaar. Mabalin nga adda rumbeng nga aramidenyo nga addang sakbay dagiti partikular a naituding nga aldaw tapno mapagtalinaedyo ti coverage ti salun-atyo wenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagsasao nga awan ti bayadanyo. Tumawag iti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):
Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbero esserci date chiave in questo avviso. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente. Chiama 800-722-1471 (TTY: 800-842-5357).

日本語 (Japanese):
この通知には重要な情報が含まれています。この通知には、Premera Blue Cross の申請または補償範囲に関する重要な情報が含まれている場合があります。この通知に記載されている可能性がある重要な日付をご確認ください。健康保険や有料サポートを維持するには、特定の期日までに行動を取らなければならない場合があります。ご希望の言語による情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。

한국어 (Korean):
본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관하여 그리고 Premera Blue Cross 를 통한 커버리지에 관한 정보를 포함하고 있을 수 있습니다. 본 통지서에는 핵심이 되는 날짜들이 있을 수 있습니다. 귀하는 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하는 이러한 정보와 도움을 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357) 로 전화하십시오.

ລາວ (Lao):
ແຈ້ງການນີ້ມີຂໍ້ມູນສຳຄັນ. ແຈ້ງການນີ້ອາດຈະມີຂໍ້ມູນສຳຄັນກ່ຽວກັບຄຳຮ້ອງສະໝັກ ຫຼື ຄວາມຄຸ້ມຄອງປະກັນໄພຂອງທ່ານຜ່ານ Premera Blue Cross. ອາດຈະມີວັນທີສຳຄັນໃນແຈ້ງການນີ້. ທ່ານອາດຈະຈຳເປັນຕ້ອງດຳເນີນການຕາມກຳນົດເວລາສະເພາະເພື່ອຮັກສາຄວາມຄຸ້ມຄອງປະກັນສຸຂະພາບ ຫຼື ຄວາມຊ່ວຍເຫຼືອເລື່ອງຄ່າໃຊ້ຈ່າຍຂອງທ່ານໄວ້. ທ່ານມີສິດໄດ້ຮັບຂໍ້ມູນນີ້ ແລະ ຄວາມຊ່ວຍເຫຼືອເປັນພາສາຂອງທ່ານໂດຍບໍ່ເສຍຄ່າ. ໃຫ້ໂທຫາ 800-722-1471 (TTY: 800-842-5357).

ភាសាខ្មែរ (Khmer):
សេចក្តីជូនដំណឹងនេះមានព័ត៌មានយ៉ាងសំខាន់។ សេចក្តីជូនដំណឹងនេះប្រហែលជាមានព័ត៌មានយ៉ាងសំខាន់អំពីទម្រង់បែបបទ ឬការរ៉ាប់រងរបស់អ្នកតាមរយៈ Premera Blue Cross ។ ប្រហែលជាមាន កាលបរិច្ឆេទសំខាន់នៅក្នុងសេចក្តីជូនដំណឹងនេះ។ អ្នកប្រហែលជាត្រូវការបញ្ចេញសមត្ថភាព ដល់កំណត់ថ្ងៃជាក់ច្បាស់នានា ដើម្បីនឹងរក្សាទុកការជានាវ៉ាប់រងសុខភាពរបស់អ្នក ឬប្រាក់ជំនួយចេញផ្លែ។ អ្នកមានសិទ្ធិទទួលព័ត៌មាននេះ និងជំនួយនៅក្នុងភាសារបស់អ្នកដោយមិនអស់លុយឡើយ។ សូមទូរស័ព្ទ 800-722-1471 (TTY: 800-842-5357)។

ਪੰਜਾਬੀ (Punjabi):
ਇਸ ਨੋਟਿਸ ਵਿਚ ਖਾਸ ਜਾਣਕਾਰੀ ਹੈ. ਇਸ ਨੋਟਿਸ ਵਿਚ Premera Blue Cross ਵਲੋਂ ਤੁਹਾਡੀ ਕਵਰੇਜ ਅਤੇ ਅਰਜੀ ਬਾਰੇ ਮਹੱਤਵਪੂਰਨ ਜਾਣਕਾਰੀ ਹੋ ਸਕਦੀ ਹੈ . ਇਸ ਨੋਜਿਸ ਜਵਚ ਖਾਸ ਤਾਰੀਖਾ ਹੋ ਸਕਦੀਆਂ ਹਨ. ਜੇਕਰ ਤੁਸੀ ਜਸਹਤ ਕਵਰੇਜ ਰਿੱਖਣੀ ਹੋਵੇ ਜਾ ਓਸ ਦੀ ਲਾਗਤ ਜਵਿੱਚ ਮਦਦ ਦੇ ਇਛੁੱਕ ਹੋ ਤਾਂ ਤੁਹਾਨੂੰ ਅੰਤਮ ਤਾਰੀਖ਼ ਤੋਂ ਪਹਿਲਾਂ ਕੁੱਝ ਖਾਸ ਕਦਮ ਚੁੱਕਣ ਦੀ ਲੋੜ ਹੋ ਸਕਦੀ ਹੈ ,ਤੁਹਾਨੂੰ ਮੁਫ਼ਤ ਵਿੱਚ ਤੇ ਆਪਣੀ ਭਾਸ਼ਾ ਵਿੱਚ ਜਾਣਕਾਰੀ ਅਤੇ ਮਦਦ ਪ੍ਰਾਪਤ ਕਰਨ ਦਾ ਅਧਿਕਾਰ ਹੈ ,ਕਾਲ 800-722-1471 (TTY: 800-842-5357).

فارسی (Farsi):
این اعلامیه حاوی اطلاعات مهم میباشد .این اعلامیه ممکن است حاوی اطلاعات مهم درباره فرم تقاضا و یا پوشش بیمه ای شما از طریق Premera Blue Cross باشد. به تاریخ های مهم در این اعلامیه توجه نمایید .شما ممکن است برای حفظ پوشش بیمه تان یا کمک در پرداخت هزینه های درمانی تان، به تاریخ های مشخصی برای انجام کارهای خاصی احتیاج داشته باشید .شما حق این را دارید که این اطلاعات و کمک را به زبان خود به طور رایگان دریافت نمایید. برای کسب اطلاعات با شماره 800-722-1471 (کاربران TTY تماس باشماره 800-842-5357) تماس برقرار نمایید.

Polskie (Polish):
To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie Państwa wniosku lub zakresu świadczeń poprzez Premera Blue Cross. Prosimy zwrócic uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utrzymania polisy ubezpieczeniowej lub pomocy związanej z kosztami. Macie Państwo prawo do bezpłatnej informacji we własnym języku. Zadzwońcie pod 800-722-1471 (TTY: 800-842-5357).

Português (Portuguese):
Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

Română (Romanian):
Prezenta notificare conține informații importante. Această notificare poate conține informații importante privind cererea sau acoperirea asigurării dumneavoastre de sănătate prin Premera Blue Cross. Pot exista date cheie în această notificare. Este posibil să fie nevoie să acționați până la anumite termene limită pentru a vă menține acoperirea asigurării de sănătate sau asistența privitoare la costuri. Aveți dreptul de a obține gratuit aceste informații și ajutor în limba dumneavoastră. Sunați la 800-722-1471 (TTY: 800-842-5357).

Русский (Russian):
Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Fa'asamoa (Samoan):
Atonu ua iai i lenei fa'asilasilaga ni fa'amatalaga e sili ona taua e tatau ona e malamalama i ai. O lenei fa'asilasilaga o se fesoasoani e fa'amatala atili i ai i le tulaga o le polokalame, Premera Blue Cross, ua e tau fia maua atu i ai. Fa'amolemole, ia e iloilo fa'alelei i aso fa'apitoa olo'o iai i lenei fa'asilasilaga taua. Masalo o le'a iai ni feau e tatau ona e faia ao le'i aulia le aso ua ta'ua i lenei fa'asilasilaga ina ia e iai pea ma maua fesoasoani mai ai i le polokalame a le Malo olo'o e iai i ai. Olo'o iai iate oe le aia tatau e maua atu i lenei fa'asilasilaga ma lenei fa'amatalaga i legagana e te malamalama i ai aunoa ma se togiga tupe. Vili atu i le telefoni 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):
Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon. Ang paunawa na ito ay maaaring naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring mangailangan ka na magsagawa ng hakbang sa ilang mga itinakdang panahon upang mapanatili ang iyong pagsakop sa kalusugan o tulong na walang gastos. May karapatan ka na makakuha ng ganitong impormasyon at tulong sa iyong wika ng walang gastos. Tumawag sa 800-722-1471 (TTY: 800-842-5357).

ไทย (Thai):
ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับการการสมัครหรือขอบเขตประกันสุขภาพของคุณผ่าน Premera Blue Cross และอาจมีกำหนดการในประกาศนี้ คุณอาจจะต้องดำเนินการภายในกำหนดระยะเวลาที่แน่นอนเพื่อจะรักษาการประกันสุขภาพของคุณหรือการช่วยเหลือที่มีค่าใช้จ่าย คุณมีสิทธิที่จะได้รับข้อมูลและความช่วยเหลือนี้ในภาษาของคุณโดยไม่มีค่าใช้จ่าย โทร 800-722-1471 (TTY: 800-842-5357)

Український (Ukrainian):
Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страхувального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дзвоніть за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):
Thông báo này cung cấp thông tin quan trọng. Thông báo này có thông tin quan trọng về đơn xin tham gia hoặc hợp đồng bảo hiểm của quý vị qua chương trình Premera Blue Cross. Xin xem ngày quan trọng trong thông báo này. Quý vị có thể phải thực hiện theo thông báo đúng trong thời hạn để duy trì bảo hiểm sức khỏe hoặc được trợ giúp thêm về chi phí. Quý vị có quyền được biết thông tin này và được trợ giúp bằng ngôn ngữ của mình miễn phí. Xin gọi số 800-722-1471 (TTY: 800-842-5357).