



**BlueCross BlueShield
of Alabama**

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Prior Authorization with Quantity Limit Program Summary

This prior authorization applies to Commercial, GenPlus, Blue Partner, NetResults A series, SourceRx and Health Insurance Marketplace formularies.

OBJECTIVE

The intent of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Prior Authorization (PA) is to encourage appropriate selection of patients for treatment according to approved labeling and/or clinical studies and/or clinical guidelines and according to dosing recommended in product labeling. Approval will require a diagnosis of cystic fibrosis or another FDA approved indication and confirmed genetic status of the CFTR mutation. Doses above the set limit will be approved if the requested quantity is below the FDA limit and cannot be dose optimized or when the quantity is above the FDA limit and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis.

TARGET AGENTS

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

QUANTITY LIMIT TARGET AGENTS- RECOMMENDED LIMITS

Brand (generic)	GPI	Multisource Code	Quantity per Day Limit
Kalydeco (ivacaftor)			
50 mg oral granules	45302030003020	M, N, O, or Y	2 packets
75 mg oral granules	45302030003030	M, N, O, or Y	2 packets
150 mg tablet	45302030000320	M, N, O, or Y	2 tablets
Orkambi (lumacaftor/ivacaftor)			
100 mg/125 mg oral granules	45309902303010	M, N, O, or Y	2 packets
100 mg/188 mg oral granules	45309902303020	M, N, O, or Y	2 packets
100 mg/125 mg tablet	45309902300310	M, N, O, or Y	4 tablets
200 mg/125 mg tablet	45309902300320	M, N, O, or Y	4 tablets
Symdeko (tezacaftor/ivacaftor and ivacaftor co-packaged)			
100 mg/150 mg tablet and 150 mg ivacaftor tablet	4530990280B720	M, N, O, or Y	2 tablets

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Initial Evaluation

The requested agent will be approved when ALL of the following are met:

1. ONE of the following:
 - A. The patient has a diagnosis of cystic fibrosis AND ALL of the following:
 - i. The patient is within the FDA labeled age for the requested agent
 - a. Kalydeco granules: 12 months through up to 6 years of age
 - b. Kalydeco tablets: 6 years of age and over

- c. Orkambi granules: 2 years through up to 6 years of age
 - d. Orkambi tablets: 6 years of age and over
 - e. Symdeko: 12 years of age and over
- AND**
- ii. The patient has *CFTR* gene mutations according to FDA label confirmed by genetic testing
 - a. Kalydeco:
 - 1. *CFTR* gene mutation: ONE mutation based on FDA label **AND**
 - 2. Does NOT have F508del mutations on BOTH alleles of *CFTR* gene (NOT homozygous)
 - b. Orkambi:
 - 1. F508del mutation on BOTH alleles of *CFTR* gene (homozygous)
 - c. Symdeko:
 - 1. *CFTR* gene mutation: ONE mutation based on FDA label **OR**
 - 2. F508del mutation on BOTH alleles of *CFTR* gene (homozygous)
- AND**
- iii. The patient has had pre-therapeutic/baseline FEV₁ levels measured
- OR**
- B. The patient has another FDA approved indication for the requested agent
- AND**
- 2. ONE of following:
 - A. The patient is NOT currently being treated with another *CFTR* agent (e.g., Kalydeco, Orkambi, Symdeko)
 - OR**
 - B. The patient is currently being treated with another *CFTR* agent AND will discontinue the other *CFTR* agent prior to starting the requested agent
- AND**
- 3. The prescriber is a specialist in cystic fibrosis or the prescriber has consulted with a specialist in cystic fibrosis
- AND**
- 4. The patient does NOT have any FDA labeled contraindications to the requested agent
- AND**
- 5. ONE of the following:
 - A. The requested quantity (dose) is NOT greater than the program quantity limit
 - OR**
 - B. ALL of the following:
 - i. The requested quantity (dose) is greater than the program quantity limit
 - AND**
 - ii. The requested quantity (dose) is less than or equal to the FDA labeled dose
 - AND**
 - iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit
 - OR**
 - C. ALL of the following:
 - i. The requested quantity (dose) is greater than the program quantity limit
 - AND**
 - ii. The requested quantity (dose) is greater than the FDA labeled dose
 - AND**
 - iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

Length of Approval: 6 months

Renewal Evaluation

The requested agent will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the Prime Therapeutics PA process
AND
2. If cystic fibrosis, the patient has shown improvement or stabilization in FEV₁ from pre-therapeutic/baseline levels
AND
3. ONE of the following:
 - a. The patient is NOT currently being treated with another CFTR agent (e.g., Kalydeco, Orkambi, Symdeko)
OR
 - b. The patient is currently being treated with another CFTR agent (e.g., Kalydeco, Orkambi, Symdeko) AND will discontinue the other CFTR agent prior to starting the requested agent**AND**
4. The prescriber is a specialist in cystic fibrosis or the prescriber has consulted with a specialist in cystic fibrosis
AND
5. The patient does NOT have any FDA labeled contraindications to the requested agent
AND
6. ONE of the following:
 - A. The requested quantity (dose) is NOT greater than the program quantity limit
OR
 - B. ALL of the following:
 - i. The requested quantity (dose) is greater than the program quantity limit
AND
 - ii. The requested quantity (dose) is less than or equal to the FDA labeled dose
AND
 - iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit**OR**
 - C. ALL of the following:
 - i. The requested quantity (dose) is greater than the program quantity limit
AND
 - ii. The requested quantity (dose) is greater than the FDA labeled dose
AND
 - iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

Length of Approval: 12 months

This pharmacy policy is not an authorization, certification, explanation of benefits or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All pharmacy policies are based on (i) information in FDA approved package inserts (and black box warning, alerts, or other information disseminated by the FDA as applicable); (ii) research of current medical and pharmacy literature; and/or (iii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

The purpose of pharmacy policies are to provide a guide to coverage. Pharmacy policies are not intended to dictate to physicians how to practice medicine. Physicians should exercise their medical judgment in providing the care they feel is most appropriate for their patients.

Neither this policy, nor the successful adjudication of a pharmacy claim, is guarantee of payment.

FDA APPROVED INDICATIONS AND DOSAGE¹⁻³

Agent	Indication	Dosing and Administration
Kalydeco® (ivacaftor)	<p>Treatment of cystic fibrosis (CF) in patients age 12 months and older who have one mutation in the <i>CFTR</i> gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data.</p> <p>If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a <i>CFTR</i> mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use</p>	<ul style="list-style-type: none"> • Pediatric patients 12 months to less than 6 years of age and weighing 7 kg to less than 14 kg: one 50 mg packet mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food • Pediatric patients 12 months to less than 6 years of age and 14 kg or greater: one 75 mg packet mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food • Adults and pediatric patients age 6 years and older: one 150 mg tablet taken orally every 12 hours with fat-containing food
Orkambi® (lumacaftor/ivacaftor)	<p>Treatment of cystic fibrosis (CF) in patients age 2 years and older who are homozygous for the <i>F508del</i> mutation in the <i>CFTR</i> gene.</p> <p>If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the <i>F508del</i> mutation on both alleles of the <i>CFTR</i> gene.</p> <p>Limitation of use: The efficacy and safety of Orkambi have not been established in patients with CF other than those homozygous for the <i>F508del</i> mutation.</p>	<ul style="list-style-type: none"> • Pediatric patients age 2 through 5 years and weighing less than 14 kg: one packet of granules (each containing lumacaftor 100 mg/ivacaftor 125 mg) mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food • Pediatric patients age 2 through 5 years and weighing 14 kg or greater: one packet of granules (each containing lumacaftor 150mg/ivacaftor 188 mg) mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food • Pediatric patients age 6 through 11 years: two tablets (each containing lumacaftor 100 mg/ivacaftor 125 mg) taken orally every 12 hours • Adults and pediatric patients age 12 years and older: two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) taken orally every 12 hours

Symdeko™ (tezacaftor/ivacaftor and ivacaftor)	<p>Treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence</p> <p>If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use</p>	<ul style="list-style-type: none"> Adults and pediatric patients ages 12 years and older: one tablet (containing tezacaftor 100 mg/ivacaftor 150 mg) in the morning and one tablet (containing ivacaftor 150 mg) in the evening, approximately 12 hours apart. Symdeko should be taken with fat-containing food
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CLINICAL RATIONALE²

Cystic Fibrosis (CF) is the most common life-threatening autosomal recessive disease in the US. CF is a multisystem disorder caused by mutations in the gene for the CF transmembrane conductance regulator (CFTR), which encodes an ion channel protein. There are more than 2000 mutations identified to date for the CFTR gene. CF is diagnosed when a patient has both clinical presentation of CF and evidence of CFTR dysfunction. Sweat chloride test should be considered first, then CFTR genetic analysis, and then CFTR physiologic tests. Diagnosis of CF can be challenging because the age of onset and severity of symptoms can differ greatly due to highly variable levels of CFTR dysfunction. Presenting manifestations can include pancreatitis, respiratory symptoms, chronic sinusitis, and male infertility.⁴ Respiratory manifestations of CF include persistent, productive cough, hyperinflation of the lung fields on chest radiograph, and pulmonary function tests that are consistent with obstructive airway disease. Infections of the airway with pathogenic bacteria occurs.⁵

There are approximately 115 CF Care Centers that comprise of physicians, nurses, dietitians, respiratory therapists, physical therapists, and social workers with special competence in CF care. Patients that receive the medical care at specialized CF centers have better clinical outcomes compared with patients followed in general community. Multi-organs systems should be considered when assessing therapies for CF. Sinus infection, nutritional status, glucose control and psychosocial issues should be assessed at regular intervals. Antibiotics, bronchodilators, anti-inflammatory agents, agents that promote airway secretion clearance, nutritional support, and CFTR modulators are possible therapies for CF patients.⁶

CFTR modulators are a new class of drugs that act by improving production, intracellular processing and/or function of the defective CFTR protein. Indications and efficacy of CFTR drugs depend upon CFTR mutations in the patient. Ivacaftor was the first approved CF therapy that restores the functioning of a mutant CF protein rather than trying to target downstream consequences. It was approved for patients who have a G551d mutation in at least one of their CFTR genes. Further clinical trials and in vitro studies have expanded the approved label for ivacaftor to 33 mutations. Combination lumacaftor and ivacaftor has showed improvements in pulmonary function and reduced the risk of pulmonary exacerbations in CF patients who are

homozygous for the F508del mutation. The F508del mutation interferes with CFTR protein folding and channel gating activity. Lumacaftor partially corrects the CFTR misfolding while ivacaftor improves the gating abnormality. Unfortunately, neither drug is effective when used alone for F508del homozygotes. In patients who are heterozygous for the F508del mutation, lumacaftor-ivacaftor does not appear to have clinically meaning benefit. Tezacaftor ivacaftor combination has shown modest improvements in pulmonary function and reduced the risk of pulmonary exacerbations for individuals who are homozygous for the F508del mutation or a heterozygous F508del mutation in combination with a residual function mutation. Tezacaftor is a CFTR corrector that improves the intracellular processing and trafficking of CFTR, while ivacaftor is a potentiator that improves the gating abnormality after CFTR is expressed in the cell surface.

For additional clinical information see the Prime Therapeutics CTL 6.5: Cystic Fibrosis.

REFERENCES

1. Kalydeco prescribing information. Vertex Pharmaceuticals Incorporated. August 2018.
2. Orkambi prescribing information. Vertex Pharmaceuticals Incorporated. August 2018.
3. Symdeko prescribing information. Vertex Pharmaceuticals Incorporated. February 2018.
4. Farrell, Philip M., MD, PhD., et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. *Journal of Pediatrics*. S4-S15.e1. February 2017. Accessed at: [http://www.jpeds.com/article/S0022-3476\(16\)31048-4/pdf](http://www.jpeds.com/article/S0022-3476(16)31048-4/pdf). Accessed February 2018.
5. Katkin, Julie P., MD, et al. Cystic Fibrosis: Clinical Manifestations and Diagnosis. UpToDate. Last updated April 2017. Literature review current through January 2018.
6. Simon, Richard H., MD, et al. Cystic Fibrosis: Overview of the Treatment of Lung Disease. UpToDate. Last updated February 2018. Literature review current through January 2018.

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