BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 5/17/18**
SECTION: DRUGS	**LAST REVIEW DATE: 9/20/18**
	LAST CRITERIA REVISION DATE: 9/20/18
	ARCHIVE DATE:

CYSTIC FIBROSIS THERAPY AGENTS:
KALYDECO® (ivacaftor) oral pack and tablet
ORKAMBI™ (lumacaftor/ivacaftor) oral granules and tablet
SYMDEKO™ (tezacaftor/ivacaftor) oral tablet therapy pack

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602)

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864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

Criteria:

- **Criteria for initial therapy:** Kalydeco (ivacaftor), Orkambi (lumacaftor-ivacaftor), and Symdeko (tezacaftor-ivacaftor) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a Gastroenterologist or Pulmonologist or other expert in care of Cystic Fibrosis patients

  2. A confirmed diagnosis of Cystic Fibrosis (CF)

  3. **For Kalydeco**: Individual is 2 years of age or older **and** has an FDA-cleared mutation test with **ONE** of the *CFTR* genes that are responsive to Kalydeco (listed in the Definition Section)

     For Orkambi: Individual is 2 years of age or older **and** has an FDA-cleared mutation test that is homozygous *F508del* mutation on both alleles of the *CFTR* gene

     For Symdeko: Individual is 12 years of age or older and **BOTH** of the following:
     - Has an FDA-cleared mutation test that is homozygous *F508del* mutation on both alleles of the *CFTR* gene **or** has at least **ONE** of the *CFTR* genes that are responsive to Symdeko (listed in the Definition Section)
     - Individual has failure, contraindication or intolerance to Orkambi

  4. **ALL** of the following baseline tests have been completed before initiation:
     - Ophthalmologic examination in pediatric patients
     - Liver enzymes that includes alanine aminotransferase (ALT) and aspartate aminotransferase (AST)

  5. **NO** dual therapy with another a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator

  Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Kalydeco (ivacaftor), Orkambi (lumacaftor-ivacaftor), and Symdeko (tezacaftor-ivacaftor) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by Gastroenterologist or Pulmonologist or other expert in care of Cystic Fibrosis patients

  2. Individual's condition responded while on therapy

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- Response is defined by one of the following:
  - Stable or improved ppFEV1 or FEV1 from baseline
  - Fewer pulmonary exacerbations
  - Stable or improved weight or BMI

3. Individual has been adherent with the medication

4. **NO** dual therapy with another a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator

5. Individual has not developed any significant level 4 adverse drug effects that may exclude continued use
   - Significant adverse effect such as:
     - Significant hepatic impairment:

6. There are no significant interacting drugs

Renewal duration: 12 months

Description:

Kalydeco (ivacaftor) is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 2 years and older who have one mutation in the *CFTR* gene that is responsive to ivacaftor based on clinical and/or in vitro assay data. 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.

Orkambi (lumacaftor-ivacaftor) is a fixed-dose combination of lumacaftor and ivacaftor indicated for the treatment of CF patients 2 years of age and older who are homozygous (having 2 copies) of the *F508del* mutation in the *CFTR* gene. 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 both alleles of the *CFTR* gene. The efficacy and safety of Orkambi (lumacaftor-ivacaftor) have not been established in patients with CF other than those homozygous for the F508del mutation.

Symdeko (tezacaftor/ivacaftor) is a combination of tezacaftor and ivacaftor, indicated for the treatment of patients with CF aged 12 years and older who are homozygous for the *F508del* mutation or who have at least one mutation in the *CFTR* gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence.

Cystic Fibrosis (CF):

- CF is a life-threatening genetic disease that causes a buildup of thick, sticky mucus that can clog the lungs and digestive tract
  - It is a rare autosomal recessive disease

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- It is estimated that approximately 30,000 people in the United States are affected

- Complications of CF include frequent lung and sinus tract infections, decreased lung function, respiratory failure, poor weight gain and growth, diabetes, liver disease, and infertility
  - Progressive lung disease is the primary cause of morbidity and mortality, ultimately resulting in respiratory failure and death
  - The primary treatment goals are maintenance of lung function over time, reduction in pulmonary exacerbations, improvement in nutritional status and improvement in quality of life

- It is hypothesized that individuals with CF have a mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that encodes an ion channel transporter, the CFTR protein
  - The CFTR protein is present on the surface of epithelial cells in multiple organs and it regulates transport of chloride and water
  - Genetic mutations can result in either an absent or defective CFTR protein that leads to accumulation of thickened mucus
  - There are more than 1,000 different mutations of the CF gene
    - The majority of CF patients are genetically homozygous for the *F508del* mutation

- In CF patients, lung function is generally monitored by spirometry measuring the forced expiratory volume in one second (FEV1) with disease severity measured by the percent of forced expiratory volume in one second (ppFEV1)
  - There is an association between (ppFEV1) and mortality based on epidemiologic models; however other factors such as annual pulmonary exacerbation rates may contribute to mortality

- Treatments aimed at CFTR gene protein abnormality:
  - Kalydeco (ivacaftor)
    - CF in patients age 2 years and older who have one mutation in the *CFTR* gene that is responsive to ivacaftor potentiation based on clinical and/or *in vitro* assay data
  - Orkambi (lumacaftor-ivacaftor)
    - CF in patients 2 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene
  - Symdeko (tezacaftor-ivacaftor)
    - CF in patients 12 years of age and older who are homozygous for the *F508del* mutation or who have one mutation in the *CFTR* gene that is responsive to tezacaftor-ivacaftor based on *in vitro* data and/or clinical evidence

- Other products are available to treat/prevent symptoms resulting from the faulty CFTR protein
  - Pulmonary infections:
    - Inhaled antibiotics [Bethkis, Kitabis Pak, TOBI, TOBI Podhaler (tobramycin), Cayston (aztreonam)]
  - Thickened secretions:
    - Mucolytics [N-acetylcysteine, Pulmozyme (dornase alpha)]
  - Digestive aids/pancreatic insufficiency:

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- Oral pancreatic enzyme supplementation [Creon, Pancreaze, Pancrelipase, Viokase, Zenpep, others]

- Other:
  - Inhaled corticosteroids
  - Inhaled bronchodilators

Definitions:

Kalydeco:

List of *CFTR* gene mutations that produce CFTR protein and are responsive to **Kalydeco**					
A455E	*E56K*	*G551S*	*R74W*	*S549N*	*2789+5G → A*
A1067T	*E193K*	*G1069R*	*R117C*	*S549R*	*3272-26A → G*
D110E	*E831X*	*G1244E*	*R117H*	*S945L*	*3849+10kbC → T*
D110H	*F1052V*	*G1349D*	*R347H*	*S977F*	
D579G	*F1074L*	*K1060T*	*R352Q*	*S1251N*	
D1152H	*G178R*	*L206W*	*R1070Q*	*S1255P*	
D1270N	*G551D*	*P67L*	*R1070W*	*711+3A → G*	

Symdeko:

List of *CFTR* gene mutations that produce CFTR protein and are responsive to **Symdeko**					
A455E	*D1152H*	*F1052V*	*P67L*	*R1070W*	*3272-26A → G*
A1067T	*D1270N*	*F1074L*	*R74W*	*S945L*	*3849+10kbC → T*
D110E	*E56K*	*F508del**	*R117C*	*S977F*	
D110H	*E193K*	*K1060T*	*R347H*	*711+3A → G*	
D579G	*E831X*	*L206W*	*R352Q*	*2789+5G → A*	
* Must have two copies of the *F508del* mutation or at least one copy of a responsive mutation presented above to be indicated.					

Resources:

Orkambi. Package Insert. Revised by manufacturer 8/20/18. Accessed 8/7/18.

Vallieres E and Elborn JS: Cystic fibrosis gene mutations: evaluation and assessment of disease severity. Advances in Genomics and Genetics 2014; 4: 161-172

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UpToDate: Cystic fibrosis: Clinical manifestations and diagnosis. Current through Sep 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/cystic-fibrosis-clinical-manifestations-and-diagnosis?source=search_result&search=cystic%20fibrosis&selectedTitle=1~150

UpToDate: Cystic fibrosis: Overview of the treatment of lung disease. Current through Sep 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/cystic-fibrosis-overview-of-the-treatment-of-lung-disease?source=related_link

UpToDate: Cystic fibrosis: Investigational therapies. Current through Sep 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/cystic-fibrosis-investigational-therapies?source=see_link

Kalydeco product information accessed 04-09-18 at DailyMed: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0ab0c9f8-3eee-4e0f-9f3f-c1e16aaffe25

Orkambi product information accessed 04-09-18 at DailyMed: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3fc1c40e-cfac-47a1-9e1a-61ead3570600

Symdeko product information accessed 04-09-18 at DailyMed: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=302ae804-37db-44fd-ac2f-3dbdeda9aa4b

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.