BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 5/17/2018**
SECTION: DRUGS	**LAST REVIEW DATE: 11/18/2021**
	LAST CRITERIA REVISION DATE: 11/18/2021
	ARCHIVE DATE:

CYSTIC FIBROSIS THERAPY AGENTS:
KALYDECO® (ivacaftor) oral
ORKAMBI™ (lumacaftor/ivacaftor) oral
SYMDEKO™ (tezacaftor/ivacaftor) oral
TRIKAFTA™ (elexacaftor/tezacaftor/ivacaftor) oral

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.

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 5/17/2018
LAST REVIEW DATE: 11/18/2021
LAST CRITERIA REVISION DATE: 11/18/2021
ARCHIVE DATE:

CYSTIC FIBROSIS THERAPY AGENTS

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) 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), Symdeko (tezacaftor-ivacaftor), or Trikafta (elexacaftor-tezacaftor-ivacaftor) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Gastroenterologist or Pulmonologist or other physician expert in care of Cystic Fibrosis patients

  2. A confirmed diagnosis of **Cystic Fibrosis (CF)**

  3. **For Kalydeco (ivacaftor)**:
     a. Individual is ***4 months of age or older*** **and** has **ONE** mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is responsive to Kalydeco based on clinical and/or *in vitro* data (listed in the Definition Section)

     For Orkambi (lumacaftor-ivacaftor):
     a. Individual is ***2 years of age or older*** **and** is **homozygous** *F508del* mutation in the *CFTR* gene

     For Symdeko (tezacaftor-ivacaftor): Individual is ***6 years of age or older*** and **BOTH** of the following:
     a. Is **homozygous** *F508del* mutation in the *CFTR* gene **or** has at least **ONE** mutation in the *CFTR* gene that is responsive to Symdeko based on clinical and/or *in vitro* data (listed in the Definition Section)
     b. Individual has failure, contraindication per FDA label or intolerance to Orkambi (lumacaftor-ivacaftor)

     For Trikafta (elexacaftor-tezacaftor-ivacaftor) ALL of the following**:**
     a. Individual is ***6 years of age or older*** **and** has at least **ONE** *F508del* mutation in the *CFTR* gene **or** a mutation in the *CFTR* gene that is responsive to Trikafta based on *in vitro* data (listed in the Definition Section)
     b. Individual has failure, contraindication per FDA label or intolerance to Orkambi (lumacaftor-ivacaftor)
     c. Individual does not have severe hepatic impairment (Child-Pugh Class C)

  4. **ALL** of the following baseline tests have been completed before initiation:
     a. FDA-cleared CF mutation test confirming *F508del* mutation or a mutation that is responsive based on *in vitro* data
     b. Ophthalmologic examination in pediatric patients

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

6. There are no significant interacting drugs

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Kalydeco (ivacaftor), Orkambi (lumacaftor-ivacaftor), Symdeko (tezacaftor-ivacaftor), or Trikafta (elexacaftor-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 a physician specializing in the patient's diagnosis or is in consultation with a Gastroenterologist or Pulmonologist or other physician expert in care of Cystic Fibrosis patients

2. Individual's condition responded while on therapy
    a. Response is defined by **ONE** of the following:
        i. Stable or improved ppFEV1 or FEV1 from baseline
        ii. Fewer pulmonary exacerbations
        iii. 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) modulator

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

6. There are no significant interacting drugs

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of a Non-cancer Medications**

2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

Description:

Kalydeco (ivacaftor) is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 4 months 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 6 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.

Trikafta (elexacaftor/tezacaftor/ivacaftor) is indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator *(CFTR)* gene.

Elexacaftor and tezacaftor bind to different sites on the CFTR protein and have an additive effect in facilitating the cellular processing and trafficking of F508del-CFTR to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. Ivacaftor potentiates the channel open probability (or gating) of the CFTR protein at the cell surface. The combined effect of elexacaftor, tezacaftor and ivacaftor is increased quantity and function of F508del-CFTR at the cell surface, resulting in increased CFTR activity as measured by CFTR mediated chloride transport.

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
    - 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

CYSTIC FIBROSIS THERAPY AGENTS

- 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)
  - Orkambi (lumacaftor-ivacaftor)
  - Symdeko (tezacaftor-ivacaftor)
  - Trikafta (elexacaftor-tezacaftor-ivacaftor)

- 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:
    - Oral pancreatic enzyme supplementation [Creon, Pancreaze, Pancrelipase, Viokase, Zenpep, others]
  - Other:
    - Inhaled corticosteroids
    - Inhaled bronchodilators

Definitions:

Kalydeco (ivacaftor):

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*	
Ivacaftor increases chloride transport in patients who carry *F508del* on one *CFTR* allele AND a second mutation predicted to be responsive to ivacaftor					
Ivacaftor did not improve lung function determined by a change in %FEV1 predicted in patients who were homozygous for *F508del* in the *CFTR* gene					

CYSTIC FIBROSIS THERAPY AGENTS

List of *CFTR* gene mutations that produce CFTR protein and are **NOT** responsive to **Kalydeco**				
A46D	*G1061R*	*L1077P*	*R560S*	*T338I*
A559T	*H1054D*	*M1101K*	*R560T*	*V520F*
A561E	*H1085R*	*N1303K*	*R1066C*	*W1282X*
E92K	*I507del*	*P205S*	*R1066H*	
G85E	*L927P*	*R334W*	*R1066M*	
G970R	*L1065P*	*R347P*	*S492F*	

Symdeko (tezacaftor-ivacaftor):

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.					

Trikafta (elexacaftor-tezacaftor-ivacaftor):

List of *CFTR* gene mutations that are responsive to **Trikafta**					
141del9	*E822K*	*G1069R*	*L967S*	*R117L*	*S912L*
546insCTA	*F191V*	*G1244E*	*L997F*	*R117P*	*S945L*
A46D	*F311del*	*G1249R*	*L1077P*	*R170H*	*S977F*
A120T	*F311L*	*G1349D*	*L1324P*	*R258G*	*S1159F*
A234D	*F508C*	*H139R*	*L1335P*	*R334L*	*S1159P*
A349V	*F508C;S1251N* *	*H199Y*	*L1480P*	*R334Q*	*S1251N*
A455E	*F508del* †	*H939R*	*M152V*	*R347H*	*S1255P*
A554E	*F575Y*	*H1054D*	*M265R*	*R347L*	*T338I*
A1006E	*F1016S*	*H1085P*	*M952I*	*R347P*	*T1036N*
A1067T	*F1052V*	*H1085R*	*M952T*	*R352Q*	*T1053I*
D110E	*F1074L*	*H1375P*	*M1101K*	*R352W*	*V201M*
D110H	*F1099L*	*I148T*	*P5L*	*R553Q*	*V232D*

CYSTIC FIBROSIS THERAPY AGENTS

D192G	*G27R*	*I175V*	*P67L*	*R668C*	*V456A*
D443Y	*G85E*	*I336K*	*P205S*	*R751L*	*V456F*
D443Y;G576A;R668C *	*G126D*	*I502T*	*P574H*	*R792G*	*V562I*
D579G	*G178E*	*I601F*	*Q98R*	*R933G*	*V754M*
D614G	*G178R*	*I618T*	*Q237E*	*R1066H*	*V1153E*
D836Y	*G194R*	*I807M*	*Q237H*	*R1070Q*	*V1240G*
D924N	*G194V*	*I980K*	*Q359R*	*R1070W*	*V1293G*
D979V	*G314E*	*I1027T*	*Q1291R*	*R1162L*	*W361R*
D1152H	*G463V*	*I1139V*	*R31L*	*R1283M*	*W1098C*
D1270N	*G480C*	*I1269N*	*R74Q*	*R1283S*	*W1282R*
E56K	*G551D*	*I1366N*	*R74W*	*S13F*	*Y109N*
E60K	*G551S*	*K1060T*	*R74W;D1270N* *	*S341P*	*Y161D*
E92K	*G576A*	*L15P*	*R74W;V201M* *	*S364P*	*Y161S*
E116K	*G576A;R668C* *	*L165S*	*R74W;V201M;D1270N* *	*S492F*	*Y563N*
E193K	*G622D*	*L206W*	*R75Q*	*S549N*	*Y1014C*
E403D	*G628R*	*L320V*	*R117C*	*S549R*	*Y1032C*
E474K	*G970D*	*L346P*	*R117G*	*S589N*	
E588V	*G1061R*	*L453S*	*R117H*	*S737F*	

* Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele
† *F508del* is a responsive *CFTR* mutation based on both clinical and *in vitro* data

Resources:

Kalydeco (ivacaftor) product information, revised by Vertex Pharmaceuticals Incorporated 12-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed September 15, 2021.

Orkambi (lumacaftor-ivacaftor) product information, revised by Vertex Pharmaceuticals Incorporated 07-2019. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed September 15, 2021.

CYSTIC FIBROSIS THERAPY AGENTS

Symdeko (tezacaftor-ivacaftor) product information, revised by Vertex Pharmaceuticals Incorporated 12-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed September 15, 2021.

Trikafta (elexacaftor-tezacaftor-ivacaftor) product information, revised by Vertex Pharmaceuticals Incorporated 06-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed September 15, 2021.

Simon RH. Cystic fibrosis: Overview of the treatment of lung disease. In: UpToDate, Mallory GB, Hoppin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed September 15, 2021.

Simon RH. Cystic fibrosis: Treatment with CFTR modulators. In: UpToDate, Mallory GB, Hoppin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed September 15, 2021.