BlueCross BlueShield Arizona

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CYSTIC FIBROSIS THERAPY AGENTS: ALYFTREK™ (vanzacaftor/tezacaftor/deutivacaftor) KALYDECO® (ivacaftor) ORKAMBI™ (lumacaftor/ivacaftor) SYMDEKO™ (tezacaftor/ivacaftor) TRIKAFTA™ (elexacaftor/tezacaftor/ivacaftor) Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

- **Criteria for initial therapy:** Alyftrek (vanzacaftor-tezacaftor-deutivacaftor), Kalydeco (ivacaftor), Orkambi (lumacaftor-ivacaftor), Symdeko (tezacaftor-ivacaftor), or Trikafta (elexacaftor-tezacaftor-ivacaftor) and/or generic equivalent (if available) are 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. Individual has a confirmed diagnosis of **Cystic Fibrosis (CF)**

3. **For Alyftrek**: **ALL** of the following:
    a. Individual is ***6 years of age or older*** **and** has at least one *F508del* mutation or another responsive mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene
    b. Individual does not have severe hepatic impairment (Child-Pugh Class C)
    c. Is **NOT** using ***moderate*** CYP3A ***inducers*** (e.g., bosentan, dabrafenib, dexamethasone, others)

4. **For Kalydeco**:
    a. Individual is ***1 months of age or older*** **and** has **ONE** mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is responsive to ivacaftor based on clinical and/or *in vitro* data (listed in the Definition section)
    b. For individuals 1 month to less than 6 months of age **BOTH** of the following:
        i. Does **NOT** have any level of hepatic impairment
        ii. Is **NOT** using ***moderate or strong*** CYP3A ***inhibitors*** (e.g., ketoconazole, fluconazole, other)

5. **For Orkambi**: **ALL** of the following:
    a. Individual is ***1 years of age or older*** **and** is **homozygous** *F508del* mutation in the *CFTR* gene
    b. Individual does not have an organ transplant or awaiting an organ transplantation
    c. Is **NOT** using midazolam, triazolam, cyclosporine, everolimus, sirolimus, tacrolimus, itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, erythromycin, telithromycin, other

6. **For Symdeko**: Individual is ***6 years of age or older*** **and** is **homozygous** *F508del* mutation in the *CFTR* gene **OR** has at least **ONE** mutation in the *CFTR* gene that is responsive to tezacaftor/ivacaftor based on clinical and/or *in vitro* data (listed in the Definition section)

7. **For Trikafta: ALL** of the following**:**
    a. Individual is ***2 years of age or older*** **and** has at least **ONE** *F508del* mutation in the *CFTR* gene **OR** has a mutation in the *CFTR* gene that is responsive to Trikafta based on *in vitro* data (listed in the Definitions section)
    b. Individual does not have severe hepatic impairment (Child-Pugh Class C)

8. Individual has completed **ALL** the following **baseline tests** before initiation of treatment and will have continued monitoring as clinically appropriate:
    a. FDA-cleared CF mutation test confirming mutation or a mutation that is responsive based on *in vitro* data
    b. Ophthalmologic examination in pediatric patients
    c. Serum transaminases (AST & ALT), alkaline phosphatase, and bilirubin

9. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

10. Alyftrek, Kalydeco, Orkambi, Symdeko, or Trikafta will **NOT** be used in combination

11. Individual does not consume grapefruit

12. There are no significant interacting drugs such as use with ***strong*** CYP3A ***inducers*** (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John's wort, other)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Alyftrek (vanzacaftor-tezacaftor-deutivacaftor), Kalydeco (ivacaftor), Orkambi (lumacaftor-ivacaftor), Symdeko (tezacaftor-ivacaftor), or Trikafta (elexacaftor-tezacaftor-ivacaftor) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

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 has documentation of positive clinical response to therapy defined as **TWO** of the following:
   a. Stable or improved ppFEV1 or FEV1 from baseline
   b. Fewer pulmonary exacerbations
   c. Stable or improved weight of BMI
   d. Reduction in sweat chloride
   e. Improvement in symptoms of cough, sputum production, and difficulty breathing

3. Individual has been adherent with the medication

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Alyftrek, Kalydeco, Orkambi, Symdeko, or Trikafta will **NOT** be used in combination

6. Individual has not developed any significant adverse drug effects that may exclude continued use such as: significant hepatic impairment

7. There are no significant interacting drugs such as use with strong CYP3A inducers (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John's wort)

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 Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

PHARMACY COVERAGE GUIDELINE

CYSTIC FIBROSIS THERAPY AGENTS

Description:

Alyftrek (vanzacaftor-tezacaftor-deutivacaftor) is a combination of deutivacaftor, a CFTR potentiator, tezacaftor, and vanzacaftor indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one *F508del* mutation or another responsive mutation in the *CFTR* gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one indicated mutation.

Kalydeco (ivacaftor) is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients aged 1 month 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 1 year 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 2 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.

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. 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 include: Kalydeco (ivacaftor), Orkambi (lumacaftor-ivacaftor), Symdeko (tezacaftor-ivacaftor), and Trikafta (elexacaftor-tezacaftor-ivacaftor). Other products are available to treat/prevent symptoms resulting from the faulty CFTR protein. For pulmonary infections: Inhaled antibiotics [Bethkis, Kitabis Pak, TOBI, TOBI Podhaler (tobramycin), Cayston (aztreonam)]. For 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 and inhaled bronchodilators.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Comparison of FDA-approved age and indication		
Kalydeco (ivacaftor)	1 mo	Who have at least **one** F508del mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data
Orkambi (lumacaftor-ivacaftor)	1 yr	Who are ***homozygous*** for the F508del mutation in the CFTR gene
Trikafta (elexacaftor-tezacaftor-ivacaftor)	2 yrs	Who have at least **one** F508del mutation in the CFTR gene **or** a mutation in the CFTR gene that is responsive based on in vitro data
Alyftrek (vanzacaftor-tezacaftor-deutivacaftor)	6 yrs	Who have at least **one** F508del mutation in the CFTR gene **or** another responsive mutation in the CFTR gene
Symdeko (tezacaftor-ivacaftor)	6 yrs	Who are ***homozygous*** for the F508del mutation in the CFTR gene **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

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					
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*
D192G	*G27R*	*I175V*	*P67L*	*R668C*	*V456A*
D443Y	*G85E*	*I336K*	*P205S*	*R751L*	*V456F*

PHARMACY COVERAGE GUIDELINE

CYSTIC FIBROSIS THERAPY AGENTS

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
Mutations that are **NOT** eligible for elexacaftor-tezacaftor-ivacaftor **but are** eligible for tezacaftor-ivacaftor are: 711+3A>G, 2789+5G>A, 3272-26A>G, 3849+10kbC>T, E831X

Resources:

Alyftrek (vanzacaftor/tezacaftor/deutivacaftor) tablets product information, revised by Vertex Pharmaceuticals Incorporated 01-2025. Available at FDA https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Accessed June 26, 2025.

Kalydeco (ivacaftor) tablets and granules product information, revised by Vertex Pharmaceuticals Incorporated 05-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 26, 2025.

Orkambi (lumacaftor-ivacaftor) tablets and granules product information, revised by Vertex Pharmaceuticals Incorporated 12-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 26, 2025.

Symdeko (tezacaftor-ivacaftor tablet and ivacaftor tablet) product information, revised by Vertex Pharmaceuticals Incorporated 01-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 26, 2025.

Trikafta (elexacaftor-tezacaftor-ivacaftor and ivacaftor) tablets and granules product information, revised by Vertex Pharmaceuticals Incorporated 12-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 26, 2025.

Katkin JP. Cystic fibrosis: Clinical manifestations and diagnosis. In: UpToDate, Chmiel JF, Hoppin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through July 2025. Topic last updated August 05, 2024. Accessed June 13, 2025.

Simon RH. Cystic fibrosis: Overview of the treatment of lung disease. In: UpToDate, Chmiel JF, Hoppin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through July 2025.Topic last updated June 25, 2025. Accessed August 13, 2025.

Simon RH. Cystic fibrosis: Treatment with CFTR modulators. In: UpToDate, Chmiel JF, Hoppin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through July 2025. Topic last updated March 20, 2025. Accessed August 13, 2025.