PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis Transmembrane Conductance Regulator – Trikafta Prior Authorization Policy
- Trikafta® (elexacaftor/tezacaftor/ivacaftor tablets; ivacaftor tablets, co-packaged and elexacaftor/tezacaftor/ivacaftor oral granules; ivacaftor oral granules, co-packaged – Vertex)

REVIEW DATE: 04/22/2026

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT WHERE APPROPRIATE AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. WHERE COVERAGE FOR CARE OR SERVICES DOES NOT DEPEND ON SPECIFIC CIRCUMSTANCES, REIMBURSEMENT WILL ONLY BE PROVIDED IF A REQUESTED SERVICE(S) IS SUBMITTED IN ACCORDANCE WITH THE RELEVANT CRITERIA OUTLINED IN THE APPLICABLE COVERAGE POLICY, INCLUDING COVERED DIAGNOSIS AND/OR PROCEDURE CODE(S). REIMBURSEMENT IS NOT ALLOWED FOR SERVICES WHEN BILLED FOR CONDITIONS OR DIAGNOSES THAT ARE NOT COVERED UNDER THIS COVERAGE POLICY (SEE "CODING INFORMATION" BELOW). WHEN BILLING, PROVIDERS MUST USE THE MOST APPROPRIATE CODES AS OF THE EFFECTIVE DATE OF THE SUBMISSION. CLAIMS SUBMITTED FOR SERVICES THAT ARE NOT ACCOMPANIED BY COVERED CODE(S) UNDER THE APPLICABLE COVERAGE POLICY WILL BE DENIED AS NOT COVERED. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Trikafta is a combination of ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, tezacaftor, and elexacaftor.[1] It is indicated for the **treatment of cystic fibrosis (CF)** in patients ≥ 2 years of age who have a clinical diagnosis of CF and who have at least one variant in the *CFTR* gene that is either responsive based on clinical and/or *in vitro* data or results in production of CFTR protein.

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one variant in the *CFTR* gene that is either responsive based on clinical and/or *in vitro* data or results in production of CFTR protein.[1]

Trikafta should only be used in patients with a clinical diagnosis of CF.[1] The presence of eligible *CFTR* variant(s) should not be the sole determinant for using Trikafta.

Guidelines

The most current treatment recommendations are the Standards of Care for CFTR variant-specific therapy for people with CF, from the European Cystic Fibrosis Society (2023).[2] However, the Standards do not reflect the currently approved age indications for Kalydeco® (ivacaftor tablets and oral granules) [≥ 1 months of age] or Orkambi® [lumacaftor/ivacaftor tablets and oral granules] (≥ 1 year of age), and do not reflect the current age or expanded indication for Trikafta (≥ 2 years of age). In general, Trikafta is recommended over other agents where indications overlap. The Standards recommend Trikafta in patients ≥ 6 years of age with CF who are homozygous or heterozygous for *F508del*. In patients with one or more responsive non-*F508del* variant, Kalydeco, Symdeko, or Trikafta are recommended. Kalydeco is recommended in patients ≥ 4 months of age with eligible *CFTR* gene variants. Orkambi is recommended for patients 2 to 5 years of age who are homozygous for *F508del*. Of note, the Standards state that after diagnosis, repeat sweat testing provides evidence of treatment effect on CFTR activity, but does not predict clinical response. The European Cystic Fibrosis Society Standards for establishing and maintaining health (2024) note that people with CF with eligible *CFTR* gene variants should be offered CFTR modulator therapy.[5]

According to the CF Foundation (2017), CF is diagnosed when an individual has both a clinical presentation of CF and evidence of CFTR dysfunction.[3,4] Clinical presentation of CF includes a positive newborn screening, signs and/or symptoms of CF, and/or family history of CF. To establish a diagnosis of CF, sweat chloride tests should be considered first, then *CFTR* genetic analysis (*CFTR* genotype), and then CFTR physiologic tests (nasal potential difference [NPD] or intestinal current measurement [ICM]). However, tests of CFTR function are not always done in this order. All individuals diagnosed with CF should have a sweat chloride test and *CFTR* genetic analysis performed.

In a patient with a sweat chloride test ≥ 60 mmol/L, CF diagnosis is established and in patients with a sweat chloride test < 30 mmol/L, a diagnosis of CF is unlikely.[3,4] Rarely, patients with a sweat chloride < 30 mmol/L may be considered to have CF if alternatives are excluded and other confirmatory tests (genetic and physiologic testing) support a CF diagnosis. In patients with a sweat chloride test of ≥ 30 to < 60 mmol/L, CFTR genetic analysis is undertaken. If the genetic analysis identifies two CF-causing *CFTR* mutations, CF is diagnosed; if no *CFTR* mutations are identified, a diagnosis of CF is unlikely. In patients with a *CFTR* genotype that is undefined or of varying clinical consequence, full gene *CFTR* sequencing (if not already performed) or CFTR physiologic testing is performed (NPD or ICM). If only one *CFTR* variant is identified on limited analysis, full gene *CFTR* sequencing should be performed. CF is possible if both alleles possess CF-causing, undefined, or mutation of varying clinical consequence mutations; CF is unlikely if only no CF-causing mutations are found. If results of the NPD or ICM show CFTR dysfunction, CF is diagnosed; when testing is unavailable or equivocal, the diagnosis of CF is not resolved, and when results of the

physiologic testing show CFTR function is preserved, a diagnosis of CF is considered unlikely. It is recommended that patients with challenging diagnoses be evaluated at an accredited CF Foundation Care Center.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Trikafta. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Trikafta as well as the monitoring required for adverse events and long-term efficacy, approval requires Trikafta to be prescribed by or in consultation with a physician who specializes in the condition being treated.

- **Trikafta® (elexacaftor/tezacaftor/ivacaftor tablets; ivacaftor tablets, co-packaged and elexacaftor/tezacaftor/ivacaftor oral granules; ivacaftor oral granules, co-packaged – Vertex)**

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indication

1. **Cystic Fibrosis.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, E, and F):
   - **A)** Patient is ≥ 2 years of age; AND
   - **B)** According to the prescriber, the patient has at least ONE variant in the cystic fibrosis transmembrane conductance regulator gene that is considered to be pathogenic or likely pathogenic; AND
   - **C)** Patient meets ONE of the following (i or ii):
     - **i.** According to the prescriber, the variant in the cystic fibrosis transmembrane conductance regulator gene is responsive to the medication based on clinical and/or *in vitro* data; OR
     - **ii.** According to the prescriber, the variant in the cystic fibrosis transmembrane conductance regulator gene results in production of cystic fibrosis transmembrane regulator protein; AND
   - **D)** Patient meets at least ONE of the following (i, ii, or iii):
     - **i.** Positive cystic fibrosis newborn screening test; OR
     - **ii.** Family history of cystic fibrosis; OR
     - **iii.** Clinical presentation consistent with signs and symptoms of cystic fibrosis; AND

       Note: Examples of clinical presentation of cystic fibrosis include but are not limited to meconium ileus, sino-pulmonary symptoms (e.g., persistent cough, wheezing, pulmonary function tests consistent with obstructive airway disease, excess sputum production), bronchiectasis, sinusitis, failure to thrive, pancreatic insufficiency.
   - **E)** Patient has evidence of abnormal cystic fibrosis transmembrane conductance regulator function as demonstrated by at least ONE of the following (i, ii, or iii):
     - **i.** Elevated sweat chloride test; OR

ii. Two cystic fibrosis-causing cystic fibrosis transmembrane conductance regulator variants; OR

iii. Abnormal nasal potential difference; AND

F) The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

CONDITIONS NOT COVERED

- **Trikafta® (elexacaftor/tezacaftor/ivacaftor tablets; ivacaftor tablets, co-packaged and elexacaftor/tezacaftor/ivacaftor oral granules; ivacaftor oral granules, co-packaged – Vertex)**

is(are) considered not medically necessary for ANY other use(s) including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Cystic Fibrosis, Patient with Unknown Cystic Fibrosis Transmembrane Conductance Regulator Gene Variant.** If the patients genotype is unknown, an FDA-cleared cystic fibrosis genetic test should be used to confirm the presence of at least one variant in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is responsive based on clinical and/or in vitro data or results in the production of CFTR protein..[1]

2. **Combination Therapy with Other Cystic Fibrosis Transmembrane Conductance Regulator Modulator(s).** Trikafta contains ivacaftor which is a component of Orkambi® (lumacaftor/ivacaftor tablets and oral granules), Kalydeco® (tablets and oral granules), and Symdeko® (tezacaftor/ivacaftor tablets; ivacaftor tablets). Tezacaftor, another component of Trikafta is also contained in Symdeko. Note: Examples of other cystic fibrosis transmembrane conductance regulator modulators are: Alyftrek® (vanzacaftor/tezacaftor/deutivacaftor tablets), Kalydeco (ivacaftor tablets and oral granules), Orkambi (lumacaftor/ivacaftor tablets and oral granules), Symdeko (tezacaftor/ivacaftor; ivacaftor tablets).

3. **Infertility.** Trikafta is indicated for the treatment of cystic fibrosis in a patient ≥ 2 years of age who have a clinical diagnosis of cystic fibrosis and who have has at least one variant in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is either responsive based on clinical and/or *in vitro* data or results in the production of CFTR protein.[1]
   Note: A patient with a diagnosis of cystic fibrosis should be reviewed using criteria for the FDA-approved indication, above.

REFERENCES

1. Trikafta® tablets and oral granules [prescribing information]. Cambridge, MA: Vertex; December 2024.
2. Southern KW, Addy C, Bell SC, et al. Standards for the care of people with cystic fibrosis; establishing and maintaining health. *J Cyst Fibros.* 2024;21-28.
3. Farrell PM, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: consensus guidelines from the Cystic Fibrosis Foundation. *J Pediatr*. 2017;181S:S4-S15.

4. Farrell PM, White TB, Howenstine MS, et al. Diagnosis of cystic fibrosis in screened populations. *J Pediatr.* 2017;181S:S33-S44.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Cystic Fibrosis (CF):** The criterion that the patient has at least one of the following mutations in the cystic fibrosis transmembrane conductance regulator gene, was modified to require that the mutation be considered pathogenic or likely pathogenic. A criterion was added to require that the patient has at least one of the following: positive cystic fibrosis newborn screening test, family history of cystic fibrosis, or a clinical presentation consistent with signs and symptoms of cystic fibrosis. A criterion was added to require that the patient has evidence of abnormal cystic fibrosis transmembrane conductance regulator function as demonstrated by at least one of the following: elevated sweat chloride test, two cystic fibrosis-causing cystic fibrosis transmembrane conductance regulator mutations, or an abnormal nasal potential difference. **Infertility:** This indication was added to Conditions Not Covered .	04/10/2024
Selected Revision	The Policy title was changed to Cystic Fibrosis Transmembrane Conductance Regulator – Trikafta PA Policy. Previously, Cystic Fibrosis – Trikafta PA Policy. **Cystic Fibrosis**: The criterion that the patient has at least one of the following mutations in the cystic fibrosis transmembrane conductance regulator gene that is considered pathogenic or likely pathogenic was updated to include 94 additional gene mutations. **Conditions Not Covered** **Cystic Fibrosis, Patient with Unknown Cystic Fibrosis Transmembrane Conductance Regulator Gene Mutation.** "Conductance" was added to the verbiage for this condition not recommended for approval. **Combination Therapy with Other Cystic Fibrosis Transmembrane Conductance Regulator Modulator(s).** This condition not recommended for approval was modified to refer to the class of cystic fibrosis transmembrane conductance regulator modulator(s). Previously individual agents were listed. A Note was added to list examples of the cystic fibrosis transmembrane conductance regulators.	01/02/2025
Annual Revision	No criteria changes.	04/09/2025
Annual Revision	**Cystic Fibrosis.** The term "mutation" was replaced by "variant" throughout the criteria. Changes to the requirements that the patient has at least ONE variant in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is considered pathogenic or likely pathogenic were made to add that this is according to the prescriber. In addition, the list of specific variants was removed. A requirement was added that, according to the prescriber, the patient either has a variant in the *CFTR* gene responsive to the medication based on clinical or *in vitro* data; OR has a variant in the *CFTR* gene results in the production of CFTR protein. **Conditions Not Covered** **Cystic Fibrosis, Patient with Unknown Cystic Fibrosis Transmembrane Conductance Regulator Gene Variant.** The	04/22/2026

	term “mutation” was replaced by “variant” in this condition not recommended for approval.	