VENTURA COUNTY
HEALTH CARE PLAN

# 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:** 04/10/2024; selected revision 01/02/2025

## OVERVIEW

Trikafta is a combination of ivacaftor, a cystic fibrosis transmembrane regulator (CFTR) potentiator, tezacaftor, and elexacaftor. It is indicated for the **treatment of cystic fibrosis (CF)** in patients ≥ 2 years of age who:

- Have at least one F508del mutation in the CFTR gene; OR
- Have a mutation in the CFTR gene that is responsive to Trikafta based on *in vitro* data.[1]

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. Table 1 lists responsive CFTR mutations based on clinical response, and/or *in vitro* data in Fischer Rat Thyroid cells or human bronchial endothelial cells, or based on extrapolation of efficacy.

**Table 1. List of CFTR Gene Mutations that are Responsive to Trikafta.[1]**

| | | | | | |
|---|---|---|---|---|---|
| *3141del9* | *F1016S* | *G628R* | *L320V* | *R170H* | *S737F* |
| *546insCTA* | *F1052V* | *G85E* | *L346P* | *R258G* | *S912L* |
| *A1006E* | *F1074L* | *G970D* | *L453S* | *R31L* | *S945L* |
| *A1067T* | *F1099L* | *H1054D* | *L967S* | *R334L* | *S977F* |
| *A120T* | *F191V* | *H1085P* | *L997F* | *R334Q* | *T1036N* |
| *A234D* | *F311del* | *H1085R* | *M1101K* | *R347H* | *T1053I* |
| *A349V* | *F311L* | *H1375P* | *M152V* | *R347L* | *T338I* |
| *A455E* | *F508C* | *H139R* | *M265R* | *R347P* | *V1153E* |
| *A46D* | *F508C;S1251N* | *H199Y* | *M952I* | *R352Q* | *V1240G* |
| *A554E* | *F508del* | *H939R* | *M952T* | *R352W* | *V1293G* |
| *D110E* | *F575Y* | *I1027T* | *P205S* | *R553Q* | *V201M* |
| *D110H* | *G1061R* | *I1139V* | *P574H* | *R668C* | *V232D* |
| *D1152H* | *G1069R* | *I1269N* | *P5L* | *R74Q* | *V456A* |
| *D1270N* | *G1244E* | *I1366N* | *P67L* | *R74W* | *V456F* |
| *D192G* | *G1249R* | *I148T* | *Q1291R* | *R74W;D1270N* | *V562I* |
| *D443Y* | *G126D* | *I175V* | *Q237E* | *R74W;V201M* | *V754M* |
| *D443Y;G576A; R668C* | *G1349D* | *I336K* | *Q237H* | *R74W;V201M; D1270N* | *W1098C* |
| *D579G* | *G178E* | *I502T* | *Q359R* | *R751L* | *W1282R* |
| *D614G* | *G178R* | *I601F* | *Q98R* | *R75Q* | *W361R* |
| *D836Y* | *G194R* | *I618T* | *R1066H* | *R792G* | *Y1014C* |
| *D924N* | *G194V* | *I807M* | *R1070Q* | *R933G* | *Y1032C* |
| *D979V* | *G27R* | *I980K* | *R1070W* | *S1159F* | *Y109N* |
| *E116K* | *G314E* | *K1060T* | *R1162L* | *S1159P* | *Y161D* |
| *E193K* | *G463V* | *L1077P* | *R117C* | *S1251N* | *Y161S* |
| *E403D* | *G480C* | *L1324P* | *R117G* | *S1255P* | *S737F* |
| *E474K* | *G551D* | *L1335P* | *R117H* | *S13F* | *S912L* |
| *E56K* | *G551S* | *L1480P* | *R117L* | *S341P* | *S945L* |
| *E588V* | *G576A* | *L15P* | *R117P* | *S364P* | |

**Table 1 (continued). List of CFTR Gene Mutations that are Responsive to Trikafta.[1]**

| | | | | | |
|---|---|---|---|---|---|
| *E60K* | *G576A;R668C* | *L165S* | *R1283M* | *S492F* | |
| *E822K* | *G622D* | *L206W* | *R1283S* | *S549N* | |
| *1507_151del9* | *2183A→G* | *2789+5G→A* | *3272-26A→G* | *3849+10kbC→T* | |
| *A107G* | *A309D* | *A262P* | *C491R* | *D1445N* | |
| *D565G* | *D993Y* | *E116Q* | *E292K* | *E403D* | |
| *F2001* | *F587I* | *G1047R* | *G1123R* | *G12474R* | |
| *G424S* | *G480S* | *G551A* | *G970S* | *H620P* | |
| *H260Q* | *H939R;H949L* | *I105N* | *I125T* | | |
| *I1331N* | *I148N* | *1506L* | *I556V* | *K162E* | |
| *L1011S* | *L137P* | *L333F* | *L333H* | *L441P* | |
| *L619S* | *M1137V* | *M150K* | *N1088D* | *N1303K* | |
| *N1303I* | *N186K* | *N187K* | *N418S* | *P140S* | |
| *P499A* | *P705L* | *Q1313K* | *Q372H* | *Q493R* | |
| *Q552P* | *R1048G* | *R117;G576A;R668C* | *R297Q* | *R31C* | |
| *R334L* | *R516S* | *F555G* | *R709Q* | *R75L* | |
| *S1045Y* | *S108F* | *S1118F* | *S1235R* | *T1086I* | |
| *T1299I* | *V392G* | *V603F* | *Y301C* | *4005+2T→C* | |
| *2789+2insA* | *3849+40A→G* | *5T;TG13* | *1341G→A* | *296+28A→G* | |
| *3849+4A→G* | *621+3A→G* | *1898+3A→G* | *3041-15T→G* | *3850-3T→G* | |
| *711+3A→G* | *2752-26A→G* | *3600G→A* | *5T;TG12* | *E831X* | |
| *F1107L* | *G27E* | *K464E* | *T1246I* | *S977F* | |

CFTR – Cystic Fibrosis Transmembrane Conductance Regulator.

## 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], Orkambi® [lumacaftor/ivacaftor tablets and oral granules] (≥ 1 year of age), or 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® (tezacaftor/ivacaftor and ivacaftor tablets), 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 CF. 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.

**Automation:** None.

## RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Trikafta is recommended in those who meet the following criteria:

### FDA-Approved Indication

1. **Cystic Fibrosis.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 2 years of age; AND
   - **B)** Patient has at least ONE of the following mutations in the cystic fibrosis conductance regulator gene that is considered to be a pathogenic or likely pathogenic variant: F508del, 3141del9, 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, 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, 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, 1507_151del9, 2183A→G, 2789+5G→A, 3272-26A→G, 3849+10kbC→T, A107G, A309D, A262P, 491R, D1445N, D565G, D993Y, E116Q, E292K, E403D, F1107L, F2001, F587I, G1047R, G1123R, G12474R, G27E, G424S, G480S, G551A, G970S, H620P, H260Q, H939R;H949L, I105N, I125T, I1331N, I148N, 1506L, I556V, K162E, K464E, L1011S, L137P, L333F, L333H, L441P, L619S, 1137V, M150K, N1088D, N1303K, N1303I, N186K,

N187K, N418S, P140S, P499A, P705L, Q1313K, Q372H, Q493R, Q552P, R1048G, R117;G576A;R668C, R297Q, R31C, R334L, R516S, F555G, R709Q, R75L, S1045Y, S108F, S1118F, S1235R, T1086I, T1246I, T1299I, V392G, V603F, Y301C, 4005+2T→C, 2789+2insA, 3849+40A→G, 5T;TG13, 1341G→A, 296+28A→G, 3849+4A→G, 621+3A→G, 1898+3A→G, 3041-15T→G, 3850-3T→G, 711+3A→G, 2752-26A→G, 3600G→A, 5T;TG12, or E831X; AND

**C)** 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.

**D)** 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 mutations; OR
- **iii.** Abnormal nasal potential difference; AND

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

## CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Trikafta is not recommended in the following situations:

1. **Cystic Fibrosis, Patient with Unknown Cystic Fibrosis Transmembrane Conductance Regulator Gene Mutation.** An FDA-cleared cystic fibrosis mutation test should be used to detect the presence of at least one indicated mutation prior to use of Trikafta.[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 has at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator gene, or has a mutation in the cystic fibrosis transmembrane conductance regulator gene that is responsive to Trikafta based on *in vitro* data.[1]
   Note: A patient with a diagnosis of cystic fibrosis should be reviewed using criteria for the FDA-approved indication, above.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

## REFERENCES

1. Trikafta® tablets [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.
5. 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.

## HISTORY

| Type of Revision | Summary of Changes | Review Date |
|---|---|---|
| Early Annual Revision | Trikafta oral granules were added to the policy.<br>**Cystic Fibrosis (CF):** The age criterion was changed to ≥ 2 years of age based on the new indication for Trikafta. | 05/03/2023 |
| 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.<br><br>**Infertility:** This indication was added to conditions not recommended for approval. | 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.<br><br>**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.<br><br>**Conditions Not Recommended for Approval**<br>**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.<br><br>**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 |