

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	
F200I	F587I	G1047R	G1123R	G12474R	
G424S	G480S	G551A	G970S	H620P	
H260Q	H939R;H949L	I105N	I125T		
I1331N	I148N	I506L	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. 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. 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. 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 Recommended for Approval 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