



PRIOR AUTHORIZATION POLICY

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

REVIEW DATE: 04/10/2024

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CIGNA NATIONAL FORMULARY COVERAGE:

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 F508del mutation. Table 1 lists responsive CFTR mutations based on *in vitro* data in Fischer Rat Thyroid cells.

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;S1251 N	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;D1270 N	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	S977F
E60K	G576A;R668C	L165S	R1283M	S492F	
E822K	G622D	L206W	R1283S	S549N	

CFTR – Cystic Fibrosis Transmembrane Regulator.

Guidelines

Guidelines from the CF Foundation (2018) provide guidance on the use of CFTR therapy in patients with CF; Trikafta is not addressed.²

According to the CF Foundation (2017), CF is diagnosed when an individual has both a clinical presentation of CF and evidence of CFTR dysfunction.^{4,5} 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.^{4,5} 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 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 1 year unless otherwise 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.

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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 (CF). 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, or S737F; 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 CF.

CONDITIONS NOT COVERED

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

is(are) considered experimental, investigational, or unproven 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 (CF), Patient with Unknown Cystic Fibrosis Transmembrane Regulator (CFTR) Gene Mutation. An FDA-cleared CF mutation test should be used to detect the presence of the CFTR mutation prior to use of Trikafta.¹

2. Combination Therapy with Orkambi, Kalydeco, or Symdeko. 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.

3. Infertility. Trikafta is indicated for the treatment of cystic fibrosis in a patient \geq 2 years of age who 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.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; August 2023.
2. Ren CL, Morgan RL, Oermann C, et al. Cystic Fibrosis Foundation Pulmonary Guidelines: Use of cystic fibrosis transmembrane conductance regulator modulator therapy in patients with cystic fibrosis. *Ann Am Thorac Soc.* 2018;15(3):271-280.
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	Trikafta oral granules were added to the policy. Cystic Fibrosis (CF): The age criterion was changed to \geq 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 Covered	04/10/2024

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