MEDICAL MUTUAL®

Drug Policy

Policy:	Trikafta (elexacaftor/tezacaftor/ivacaftor; ivacaftor)	Annual Review Date: 01/16/2025 Last Revised Date: 01/16/2025

OVERVIEW

Trikafta is a combination of ivacaftor, a cystic fibrosis transmembrane regulator (CFTR) potentiator, tezacaftor, and elexacaftor 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 a mutation in the CFTR gene that is responsive to Trikafta based on in vitro data. 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 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.
CFTR – Cystic Fibrosis Transmembrane Regulator.

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

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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	
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	

POLICY STATEMENT

This policy involves the use of Trikafta. Prior authorization is recommended for pharmacy benefit coverage of Trikafta. Approval is recommended for those who meet the conditions of coverage in the **Criteria and Initial/Extended Approval** for the diagnosis provided. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria. Requests for uses not listed in this policy will be reviewed for evidence of efficacy and for medical necessity on a case-by-case basis.

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, initial approval requires Trikafta be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is allowed, a response to therapy is required for continuation of therapy unless otherwise noted below.

RECOMMENDED AUTHORIZATION CRITERIA

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

1. **Cystic Fibrosis (CF); initial use**
   Criteria. *Patient must meet the following criteria (A, B, C, D, and E):*

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A. The patient is 2 years of age or older; AND
B. Trikafta is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of CF; AND
C. The patient meets ONE of the following (i or ii):
  i. The patient has at least one copy of the F508del mutation in the CFTR gene; OR
  ii. The patient has at least one specific mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) gene that laboratory testing shows is susceptible to treatment with Trikafta (Note: See Table 1 above for list of mutations); 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 mutations; OR
  iii. Abnormal nasal potential difference

2. Cystic Fibrosis (CF); continuation of therapy
Criteria. *Patient must meet the following criteria (A, B, C, and D):*

A. The patient continues to meet all criteria in (1) above for new starts; AND
B. The patient has been using Trikafta for at least 6 months; AND
C. The patient has experienced an adequate response to therapy (e.g. improvement in FEV1 and/or other lung function tests, improvement in sweat chloride, decrease in pulmonary exacerbations or infections, increase in weight, decrease in hospitalizations, etc.) compared to baseline.

Initial Approval/ Extended Approval
A) *Initial Approval:* 6 months
B) *Extended Approval:* 1 year

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Trikafta has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

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1. **Cystic Fibrosis (CF), Patients 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.

2. **Combination Therapy with Other Cystic Fibrosis Transmembrance 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 $\geq$ 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 conductance regulator gene that is response to Trikafta based on *in vitro* data.[1]

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

Documentation Requirements:

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drug provided or services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

REFERENCES

1. Trikafta™ tablets [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; June 2019.
2. Kalydeco™ tablets and oral granules [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; April 2019.
3. Orkambi™ tablets and oral granules [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; July 2019.
4. Symdeko™ tablets [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; June 2019.
5. Ren CL, Morgan RL, Oermann C, et al. Cystic Fibrosis Foundation Pulmonary Guidelines: Use of cystic fibrosis trasmembrane conductance regulator modulator therapy in patients with cystic fibrosis. *Ann Am Thorac Soc*. 2018;15(3):271-280.
6. CF patient registry 2017. Available at: https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2017-Patient-Registry-Annual-Data-Report.pdf. Accessed on October 22, 2019.
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