

Clinical Policy: Elexacaftor/Ivacaftor/Tezacaftor; Ivacaftor (Trikafta)

Reference Number: ERX.SPA.357

Effective Date: 12.01.19

Last Review Date: 02.21

Line of Business: Commercial, Medicaid

[Revision Log](#)

See **Important Reminder** at the end of this policy for important regulatory and legal information.

Description

Elexacaftor/ivacaftor/tezacaftor (Trikafta[™]) is a triple combination drug for cystic fibrosis (CF).

- Elexacaftor and tezacaftor bind to different sites on the cystic fibrosis transmembrane conductance regulator (CFTR) protein and have an additive effect in facilitating the cellular processing and trafficking of F508del-CFTR to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone.
- Ivacaftor potentiates the channel open probability (or gating) of the CFTR protein at the cell surface.
- The combined effect of elexacaftor, tezacaftor, and ivacaftor is increased quantity and function of F508del-CFTR at the cell surface, resulting in increased CFTR activity as measured by CFTR mediated chloride transport.

FDA Approved Indication(s)

Trikafta is indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one *F508del* mutation in the *CFTR* gene or a mutation in the *CFTR* gene that is responsive 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 or a mutation that is responsive based on *in vitro* data.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions[™] that Trikafta is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Cystic Fibrosis (must meet all):

1. Diagnosis of CF confirmed by all of the following (a, b, and c):
 - a. Clinical symptoms consistent with CF in at least one organ system, or positive newborn screen or genetic testing for siblings of patients with CF;
 - b. Evidence of CFTR dysfunction confirmed by one of the following (i or ii) (*see Appendix D*):
 - i. Elevated sweat chloride > 60 mmol/L;
 - ii. Genetic testing confirming the presence of two disease-causing mutations in CFTR gene, one from each parental allele;
 - c. Confirmation of one of the following (i or ii):
 - i. Member has at least one *F508del* mutation in the CFTR gene;
 - ii. Member has a mutation in the CFTR gene that is responsive to Trikafta based on *in vitro* data (*see Appendix E*);
2. Age ≥ 6 years;
3. Prescribed by or in consultation with a pulmonologist;

4. Chart notes indicate that pulmonary function tests, performed within the last 90 days, show a percent predicted forced expiratory volume in 1 second (ppFEV1) that is between 40-90%;
5. Trikafta is not prescribed concurrently with other CFTR modulators (e.g., Orkambi®, Kalydeco®, Symdeko®);
6. Dose does not exceed (a or b):
 - a. Age 6 to < 12 years and weight < 30 kg: elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 150 mg (2 tablets elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg and 1 tablet ivacaftor 75 mg) per day;
 - b. Age 6 to < 12 years and weight ≥ 30 kg, or age ≥ 12 years: elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 300 mg (2 tablets elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg and 1 tablet ivacaftor 150 mg) per day.

Approval duration: 4 months

B. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Cystic Fibrosis (must meet all):

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. If member has received at least 12 weeks of therapy, member is responding positively to therapy as evidenced by stabilization in ppFEV1 if baseline was ≥ 70% or increase in ppFEV1 if baseline was < 70%;
3. Trikafta is not prescribed concurrently with other CFTR modulators (e.g., Orkambi, Kalydeco, Symdeko);
4. If request is for a dose increase, new dose does not exceed (a or b):
 - a. Age 6 to < 12 years and weight < 30 kg: elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 150 mg (2 tablets elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg and 1 tablet ivacaftor 75 mg) per day;
 - b. Age 6 to < 12 years and weight ≥ 30 kg, or age ≥ 12 years: elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 300 mg (2 tablets elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg and 1 tablet ivacaftor 150 mg) per day.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2):

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

- A.** Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ACFLD: advanced cystic fibrosis lung disease

CF: cystic fibrosis

CFF: Cystic Fibrosis Foundation

CFTR: cystic fibrosis transmembrane conductance regulator

FDA: Food and Drug Administration

ppFEV1: percent predicted forced expiratory volume in 1 second

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: Contraindications/Boxed Warnings
None reported

Appendix D: General Information

- Regarding the diagnostic criteria for CF:
 - The Cystic Fibrosis Foundation (CFF) guidelines state that CFTR dysfunction needs to be confirmed with an elevated sweat chloride ≥ 60 mmol/L.
 - “Genetic testing confirming the presence of two disease-causing mutations in CFTR gene” is used to ensure that whether heterozygous or homozygous, there are two disease-causing mutations in the CFTR gene, one from each parental allele. One of those two mutations must be an *F508del* mutation but does not necessarily require both.
- Most children can do spirometry by age 6, though some preschoolers are able to perform the test at a younger age. Some young children aren’t able to take a deep enough breath and blow out hard and long enough for spirometry. Forced oscillometry is another way to test lung function in young children. This test measures how easily air flows in the lungs (resistance and compliance) with the use of a machine.
- CFF 2020 guidelines for advanced cystic fibrosis lung disease (ACFLD):
 - Define ACFLD as ppFEV1 $< 40\%$ when stable or referred for lung transplantation evaluation or previous intensive care unit (ICU) admission for respiratory failure, hypercarbia, daytime oxygen requirement at rest (excluding nocturnal use only), pulmonary hypertension, severe functional impairment from respiratory disease (New York Heart Association Class IV), six-minute walk test distance < 400 m.
 - No recommendations on the start or continuation of CFTR modulator therapy with ACFLD guidelines.
 - Treatment recommendations included: lung transplantation, supplemental oxygen, continuous alternating inhaled antibiotics, and systemic corticosteroids.

Appendix E: CFTR Gene Mutations that are Responsive to Trikafta

CFTR Gene Mutations that are Responsive to Trikafta					
<i>3141del9</i>	<i>E822K</i>	<i>G1069R</i>	<i>L967S</i>	<i>R117L</i>	<i>S912L</i>
<i>546insCTA</i>	<i>F191V</i>	<i>G1244E</i>	<i>L997F</i>	<i>R117P</i>	<i>S945L</i>
<i>A46D</i>	<i>F311del</i>	<i>G1249R</i>	<i>L1077P</i>	<i>R170H</i>	<i>S977F</i>
<i>A120T</i>	<i>F311L</i>	<i>G1349D</i>	<i>L1324P</i>	<i>R258G</i>	<i>S1159F</i>
<i>A234D</i>	<i>F508C</i>	<i>H139R</i>	<i>L1335P</i>	<i>R334L</i>	<i>S1159P</i>
<i>A349V</i>	<i>F508C;</i> <i>S1251N[†]</i>	<i>H199Y</i>	<i>L1480P</i>	<i>R334Q</i>	<i>S1251N</i>
<i>A455E</i>	<i>F508del</i>	<i>H939R</i>	<i>M152V</i>	<i>R347H</i>	<i>S1255P</i>
<i>A554E</i>	<i>F575Y</i>	<i>H1054D</i>	<i>M265R</i>	<i>R347L</i>	<i>T338I</i>
<i>A1006E</i>	<i>F1016S</i>	<i>H1085P</i>	<i>M952I</i>	<i>R347P</i>	<i>T1036N</i>
<i>A1067T</i>	<i>F1052V</i>	<i>H1085R</i>	<i>M952T</i>	<i>R352Q</i>	<i>T1053I</i>
<i>D110E</i>	<i>F1074L</i>	<i>H1375P</i>	<i>M1101K</i>	<i>R352W</i>	<i>V201M</i>
<i>D110H</i>	<i>F1099L</i>	<i>I148T</i>	<i>P5L</i>	<i>R553Q</i>	<i>V232D</i>
<i>D192G</i>	<i>G27R</i>	<i>I175V</i>	<i>P67L</i>	<i>R668C</i>	<i>V456A</i>
<i>D443Y</i>	<i>G85E</i>	<i>I336K</i>	<i>P205S</i>	<i>R751L</i>	<i>V456F</i>
<i>D443Y;G576A;</i> <i>R668C[†]</i>	<i>G126D</i>	<i>I502T</i>	<i>P574H</i>	<i>R792G</i>	<i>V562I</i>
<i>D579G</i>	<i>G178E</i>	<i>I601F</i>	<i>Q98R</i>	<i>R933G</i>	<i>V754M</i>
<i>D614G</i>	<i>G178R</i>	<i>I618T</i>	<i>Q237E</i>	<i>R1066H</i>	<i>V1153E</i>
<i>D836Y</i>	<i>G194R</i>	<i>I807M</i>	<i>Q237H</i>	<i>R1070Q</i>	<i>V1240G</i>
<i>D924N</i>	<i>G194V</i>	<i>I980K</i>	<i>Q359R</i>	<i>R1070W</i>	<i>V1293G</i>
<i>D979V</i>	<i>G314E</i>	<i>I1027T</i>	<i>Q1291R</i>	<i>R1162L</i>	<i>W361R</i>

CFTR Gene Mutations that are Responsive to Trikafta					
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	

[†] Complex/compound mutations where a single allele of the CFTR gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
CF	<p>Pediatric patients age 6 years to less than 12 years weighing less than 30 kg:</p> <ul style="list-style-type: none"> <u>Morning dose</u>: 2 tablets (each containing elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg) <u>Evening dose</u>: 1 tablet of ivacaftor 75 mg <p>Adults, pediatric patients age 12 years and older, or pediatric patients age 6 years to less than 12 years weighing 30 kg or more:</p> <ul style="list-style-type: none"> <u>Morning dose</u>: 2 tablets (each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) <u>Evening dose</u>: 1 tablet of ivacaftor 150 mg <p>Morning and evening dose should be taken PO approximately 12 hours apart with fat-containing food</p>	<p>elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 150 mg per day</p> <p>elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 300 mg per day</p>

VI. Product Availability

Tablets: co-packaged fixed dose combination containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg and ivacaftor 150 mg; co-packaged fixed dose combination containing elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg and ivacaftor 75 mg

VII. References

1. Trikafta Prescribing Information. Boston, MA: Vertex Pharmaceuticals, Inc.; June 2021. Available at: <https://www.trikafta.com/>. Accessed June 15, 2021.
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.
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4. Goss CH, Burns JL. Exacerbations in cystic fibrosis. 1: Epidemiology and pathogenesis. *Thorax*. 2007;62(4):360–367.
5. Flume PA, Mogayzel PJ Jr, Robinson KA, et al. Clinical Practice Guidelines for Pulmonary Therapies Committee. Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. *Am J Respir Crit Care Med*. 2009 Nov 1;180(9):802-8.
6. Kapnadak SG, Dimango E, Hadjiliadis D, et al. Cystic Fibrosis Foundation consensus guidelines for the care of individuals with advanced cystic fibrosis lung disease. *J Cyst Fibros*. 2020 May;19(3):344-354.

7. Mogayzel PJ Jr, Naureckas ET, Robinson KA, et al. Pulmonary Clinical Practice Guidelines Committee. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2013 Apr 1;187(7):680-9.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	10.29.19	11.19
1Q 2020 annual review: for initial approval: added comprehensive diagnostic criteria to confirm CF diagnosis (e.g., clinical symptoms in at least one organ, positive newborn screen, siblings genetic testing, and evidence of CFTR dysfunction confirmed by sweat chloride or genetic testing); updated pulmonary function tests to show ppFEV1 that is between 40-90%; added in vitro testing demonstrates a baseline chloride transport < 10% of wild type CFTR; added requirement for lack of responsiveness to other CFTR modulators; added for members currently using another CFTR modulator switching to Trikafta must show increase in chloride transport of < 10% over baseline; for continued therapy: added positive response after at least 12 weeks of therapy of a) stabilization in ppFEV1 in lieu of an increase is acceptable if baseline was ≥ 70% and b) chloride transport ≥ 10% since baseline; modified initial approval duration to 4 months with reauthorization for 12 months; added Appendix D.	12.17.19	02.20
Clarified continuation of therapy requires an increase in chloride transport of 10% or greater.	02.11.20	
Revised initial approval criteria: evidence of clinical severity as defined by an average sweat chloride > 86 mmol/L to > 60 mmol/L; removed in vitro testing demonstrates a baseline chloride transport < 10% of wild type CFTR; removed requirement for lack of responsiveness to other CFTR modulators; removed for members currently using another CFTR modulator switching to Trikafta must show increase in chloride transport of < 10% over baseline; removed positive response after at least 12 weeks of therapy of b) chloride transport ≥ 10% since baseline requirement; revised Appendix D.	04.22.20	08.20
1Q 2021 annual review: RT4: based on the updated indication and gene mutations responsive to Trikafta, added diagnosis criteria option for member to have a mutation in the CFTR gene that is responsive to Trikafta, in addition to the previous requirement of member having one F508del mutation in the CFTR gene, with a reference to new addition of Appendix E; revised verbiage in criteria to align with other CF policies; updated Appendix D; references reviewed and updated.	01.19.21	02.21
RT4: revised to include pediatric expansion and new dose strength.	06.15.21	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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CLINICAL POLICY

Elexacaftor/Ivacaftor/Tezacaftor; Ivacaftor



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