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

Reference Number: GA.PMN.04
Effective Date: 10/2021
Last Review Date: 10/2021
Line of Business: 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.

It is the policy of health plans affiliated with Centene Corporation® 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. Trikafta is not prescribed concurrently with other CFTR modulators (e.g., Orkambi®, Kalydeco®, Symdeko®);
5. 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 the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Cystic Fibrosis (must meet all)**:**

1. Currently receiving medication via Centene benefit 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 Centene benefit and documentation supports positive response to therapy.

Approval duration: Duration of request or 6 months (whichever is less); or

2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid 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 < 400m.

- 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

List of CFTR Gene Mutations that are Responsive to Trikafta					
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	*F508del*	*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*	

† 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	Pediatric patients age 6 years to less than 12 years weighing less than 30 kg: • Morning dose: 2 tablets (each containing elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg) • Evening dose: 1 tablet of ivacaftor 75 mg Adults, pediatric patients age 12 years and older, or pediatric patients age 6 years to less than 12 years weighing 30 kg or more: • Morning dose: 2 tablets (each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) • Evening dose: 1 tablet of ivacaftor 150 mg Morning and evening dose should be taken PO approximately 12 hours apart with fat-containing food	elexacaftor 100 mg/ tezacaftor 50 mg/ ivacaftor 150 mg per day elexacaftor 200 mg/ tezacaftor 100 mg/ ivacaftor 300 mg per day

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.
3. Farrell PM, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: consensus guidelines from the Cystic Fibrosis Foundation. J Pediatr. 2017 Feb;181S:S4-S15.e1.
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	10/2021	10/2021

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.