09-J3000-53

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Reviewed: 04/10/24

Revised: 05/15/24

Next Review: 04/09/25

Subject: Elexacaftor-tezacaftor-ivacaftor (Trikafta)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Elexacaftor, tezacaftor, and ivacaftor combination therapy was approved by the U.S. Food and Drug Administration (FDA) in 2019 for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR).

Elexacaftor, tezacaftor, and ivacaftor increase the quantity and function of the CFTR protein, a chloride channel present at the surface of epithelial cells in multiple organs, resulting in increases in chloride transplant. In patients with the *F508del* mutation, CFTR protein misfolding causes a defect in cellular processing and trafficking that targets the protein for degradation, resulting in a lower quantity of CFTR at the cell surface. The small amount of *F508del*-CFTR that does reach the cell surface is less stable and has low channel-open probability compared to the wild-type CFTR protein. Elexacaftor and tezacaftor facilitate the cellular processing and trafficking of normal and select mutant forms of CFTR (including *F508del*-CFTR) to increase the amount of mature CFTR protein delivered to the cell surface. Ivacaftor is a CFTR potentiator that increases chloride transport by potentiating the channel-opening probability of the CFTR protein. CFTR protein must be present at the cell surface for ivacaftor to function. Ivacaftor can potentiate the CFTR protein delivered to the cell surface by tezacaftor, leading to a further enhancement of chloride transport than either agent alone.

The efficacy and safety of elexacaftor in combination with tezacaftor plus ivacaftor was evaluated in participants with cystic fibrosis homozygous for the F508del mutation, aged 12 years or older with stable disease, and with a percentage predicted forced expiratory volume in 1 s (ppFEV1) of 40–90%, inclusive. After a 4-week tezacaftor plus ivacaftor run-in period, participants were randomly assigned (1:1) to 4 weeks of elexacaftor 200 mg-tezacaftor 100 mg once daily plus ivacaftor 150 mg twice daily (n=55) or tezacaftor 100 mg once daily plus ivacaftor 150 mg twice daily (n=52). The primary outcome was the absolute change from baseline (measured at the end of the tezacaftor plus ivacaftor run-in) in

ppFEV1 at week 4. Key secondary outcomes were absolute change in sweat chloride and Cystic Fibrosis Questionnaire-Revised respiratory domain (CFQ-R RD) score.

The elexacaftor plus tezacaftor plus ivacaftor group had improvements in the primary outcome of ppFEV1 (least squares mean [LSM] treatment difference of 10.0 percentage points [95% CI 7.4 to 12.6], p<0.0001) and the key secondary outcomes of sweat chloride concentration (LSM treatment difference −45.1 mmol/L [95% CI −50.1 to −40.1], p<0.0001), and CFQ-R RD score (LSM treatment difference 17.4 points [95% CI 11.8 to 23.0], p<0.0001) compared with the tezacaftor plus ivacaftor group. The triple combination regimen was well tolerated, with no discontinuations. Most adverse events were mild or moderate; serious adverse events occurred in two (4%) participants receiving elexacaftor plus tezacaftor plus ivacaftor and in one (2%) receiving tezacaftor plus ivacaftor.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of elexacaftor-tezacaftor-ivacaftor (Trikafta™) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member is diagnosed with cystic fibrosis (CF)
2. Member meets **ONE** of the following:
    a. Member has at least one F508 del mutation in the CF transmembrane conductance regulator (CFTR) gene confirmed by an FDA-cleared cystic fibrosis mutation test – laboratory documentation must be provided
    b. Member has at least one mutation in the CFTR gene confirmed by an FDA-cleared cystic fibrosis mutation test that is responsive to treatment with elexacaftor-tezacaftor-ivacaftor per the FDA-approved label (Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f354423a-85c2-41c3-a9db-0f3aee135d8d – see CLINICAL PHARMACOLOGY (12.1)) – laboratory documentation must be provided
3. Elexacaftor-tezacaftor-ivacaftor is not administered in combination with single-agent ivacaftor (Kalydeco), lumacaftor-ivacaftor (Orkambi), or tezacaftor-ivacaftor co-packaged with ivacaftor (Symdeko™)
4. Dose does not exceed three tablets per day
5. One of the following:
    a. Member is 2 years of age or older
    b. Member's age is within FDA approved labeling

Approval duration: 6 months

Continuation of elexacaftor-tezacaftor-ivacaftor (Trikafta™) **meets the definition of medical necessity** for members meeting **ALL** of the following criteria:

1. Authorization/reauthorization has been previously approved by Florida Blue **OR** the member has previously met all indication-specific initiation criteria
2. Member meets **ONE** of the following:
    a. Member demonstrates a clinically meaningful response to treatment with elexacaftor-tezacaftor-ivacaftor as indicated by any of the following:
        i. Improvement in forced expiratory volume in one second (FEV1) – documentation must be provided
        ii. Improvement in body mass index (BMI) – documentation must be provided
        iii. Reduction in pulmonary exacerbations – documentation must be provided
        iv. Improvement in quality of life as demonstrated by Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score – documentation must be provided
    b. Member currently demonstrates a beneficial response to treatment with tezacaftor-ivacaftor **AND** has been receiving treatment with an ivacaftor-based regimen (Symdeko, Kalydeco, Orkambi) for a minimum of 18 months
3. Elexacaftor-tezacaftor-ivacaftor is not administered in combination with single-agent ivacaftor (Kalydeco), lumacaftor-ivacaftor (Orkambi), or tezacaftor-ivacaftor co-packaged with ivacaftor (Symdeko™)
4. Dose does not exceed
    a. Adults and children 6 years and older: three tablets per day
    b. Children 2 years to less than 6 years old: two packets per day
5. One of the following:
    a. Member is 2 years of age or older
    b. Member's age is within FDA approved labeling

Approval duration: 1 year

NOTE: If the member's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of any mutation. Quest Diagnostics® can perform the CF mutation test. Additionally, documentation of member's mutation from the Cystic Fibrosis Foundation CF Patient Registry is acceptable in place of original laboratory documentation.

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Adults and pediatric patients aged 12 years and older:
    - Morning dose: two elexacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg tablets
    - Evening dose: one ivacaftor 150 mg tablet
- 6 to less than12 years weighing 30 kgs or more
    - Morning dose: two elexacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg tablets
    - Evening dose: one ivacaftor 150 mg tablet
- 6 to less than 12 years weighing less than 30 kgs
    - Morning dose: two elexacaftor 50 mg, tezacaftor 25 mg and ivacaftor 37.5 mg tablets
    - Evening dose: one ivacaftor 75 mg tablet
- 2 to less than 6 years weighing 14 kg or more:
    - Morning dose: One packet (containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) oral granules
    - Evening dose: One packet (containing ivacaftor 75 mg) oral granules
- 2 to less than 6 years weight less than 14 kg:
    - Morning dose: One packet (containing elexacaftor 80 mg/tezacaftor 40 mg/ivacaftor 60 mg) oral granules
    - Evening dose: One packet (containing ivacaftor 59.5 mg) oral granules
- Morning and evening dose should be taken approximately 12 hours apart with fat-containing food

Dose Adjustments

- Reduce dose when co-administered with drugs that are moderate or strong CYP3A inhibitors

Drug Availability

- Tablets:
    - Fixed-dose combination containing elexacaftor 50 mg, tezacaftor 25 mg and ivacaftor 37.5 mg co-packaged with ivacaftor 75 mg
    - Fixed-dose combination containing elexacaftor 100 mg, tezacaftor 50 mg, and ivacaftor 75 mg co-packaged with ivacaftor 150 mg
- Oral granules:
    - Unit-dose packets of elexacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg co-packaged with unit-dose packets of ivacaftor 75 mg
    - Unit-dose packets of elexacaftor 80 mg, tezacaftor 40 mg and ivacaftor 60 mg co-packaged with unit-dose packets of ivacaftor 59.5 mg

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- Elevated liver function tests (ALT, AST or bilirubin): Liver function tests (ALT, AST, and bilirubin) should be assessed prior to initiating TRIKAFTA, every 3 months during the first year of treatment, and annually thereafter. In patients with a history of hepatobiliary disease or liver function test elevations, more frequent monitoring should be considered. Dosing should be interrupted in patients with ALT or AST >5 × upper limit of normal (ULN) or ALT or AST >3 × ULN with bilirubin >2 × ULN. Following resolution of transaminase elevations, consider the benefits and risks of resuming treatment.
- Use with CYP3A inducers: Concomitant use with strong CYP3A inducers (e.g., rifampin, St. John's wort) significantly decrease ivacaftor exposure and are expected to decrease elexacaftor and tezacaftor exposure, which may reduce TRIKAFTA efficacy. Therefore, co-administration is not recommended.
- Cataracts: Non-congenital lens opacities/cataracts have been reported in pediatric patients treated with ivacaftor-containing regimens. Baseline and follow-up examinations are recommended in pediatric patients initiating TRIKAFTA treatment.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

ICD-10 Diagnosis Codes That Support Medical Necessity

E84.0	Cystic fibrosis with pulmonary manifestations
E84.11	Meconium ileus in cystic fibrosis
E84.19	Cystic fibrosis with other intestinal manifestations
E84.8	Cystic fibrosis with other manifestations
E84.9	Cystic fibrosis, unspecified

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

None

RELATED GUIDELINES

Genetic Testing, 05-82000-28

Ivacaftor (Kalydeco TM) Oral, 09-J1000-68

Lumacaftor/Ivacaftor (Orkambi) Capsule, 09-J2000-29

Tezacaftor/Ivacaftor (Symdeko), 09-J2000-97

OTHER:

None

REFERENCES:

1. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2024 [cited 4/1/24]. Available from: http://www.clinicalpharmacology.com/.
2. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29 - [cited 4/1/24]. Available from: http://clinicaltrials.gov/.
3. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 4/1/24].
4. Heijerman HGM, McKone EF, Downey DG, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. Lancet. 2019 Oct 30. pii: S0140-6736(19)32597-8.
5. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2024 [cited 4/1/24]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.
6. Vertex. TRIKAFTA (elexacaftor, tezacaftor, and ivacaftor) kit. 2021 [cited 4/1/21]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine. Available from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f354423a-85c2-41c3-a9db-0f3aee135d8d

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 04/10/24.

GUIDELINE UPDATE INFORMATION:

12/15/19	New Medical Coverage Guideline.
05/15/20	Review and revision; updated references.
05/15/21	Review and revision; updated references.
07/15/21	Revision to position statement.
05/15/24	Review and revision; updated position statement, dosing, references.