09-J5000-10

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Reviewed: 02/12/25

Revised: 00/00/00

Subject: Deutivacaftor-Tezacaftor-Vanzacaftor (Alyftrek™)

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DESCRIPTION:

Vanzacaftor/tezacaftor/deutivacaftor (Alyftrek) combination fixed-dose tablets were approved by the U.S. Food and Drug Administration (FDA) in 2024 for use in patients aged 6 years and older with cystic fibrosis (CF) who have at least one F508del mutation or another responsive mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. An FDA-cleared test should be used to confirm the presence of an indicated mutation if the patient's genotype is unknown.

Vanzacaftor/tezacaftor/deutivacaftor is a CFTR modulator. It works by enhancing the function of the CFTR protein, a chloride channel present at the surface of epithelial cells in multiple organs, resulting in increases in chloride transplant. Vanzacaftor binds to a site on the CFTR protein (different from where tezacaftor binds) and has an additive effect in facilitating the cellular process and trafficking of select mutant forms of CFTR (including F508del-CFTR) to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. Tezacaftor binds to a site on the CFTR protein and has an additive effect in facilitating the cellular process and trafficking of select mutant forms of CFTR (including F508del-CFTR) to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. Deutivacaftor potentiates the channel open probability of the CFTR protein at the cell surface.

The efficacy and safety of vanzacaftor/tezacaftor/deutivacaftor (Van/Tez/Deut) were evaluated in two randomized, double-blind, active controlled Phase 3 clinical trials. Both trials enrolled patients with at least one F508del mutation or other mutation responsive to triple combination CFTR modulators. In trial 1 (SKYLINE 102, NCT05033080), patients that were heterozygous for F508del and a minimal function mutation were initially treated with elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 150 mg (Elx/Tez/Iva; Trikafta) in the morning and ivacaftor 150 mg in the evening for 4 weeks before being randomized to continue the same treatment (n=202) or switch to vanzacaftor 20 mg/tezacaftor 100

mg/deutivacaftor 250 mg (n=196). The primary endpoint was mean absolute change in ppFEV1 from baseline through Week 24. A key secondary endpoint was mean absolute change in SwCl from baseline through Week 24. At Week 24, Van/Tez/Deut showed non-inferiority in terms of improving lung function (comparing mean absolute change in ppFEV1 from baseline).

In Trial 2 (SYLINE 103, NCT05076149), patients with F508del-F508del, F508del-residual function, F508del-gating, or Trikafta-responsive, non-F508del genotypes underwent a similar 4-week run-in period described in Trial 1 above. Patients were randomized to continue treatment with Elx/Tez/Iva (n=289) or switch to treatment with Van/Tez/Deut (n=284). The primary endpoint was mean absolute change in ppFEV1 from baseline through Week 24. A key secondary endpoint was mean absolute change in SwCl from baseline through Week 24. At Week 24, Van/Tez/Deut showed non-inferiority in terms of improving lung function (comparing mean absolute change in ppFEV1 from baseline).

Both studies showed a significant difference in sweat chloride reduction between treatments, although the study was not designed to assess this difference. A summary of efficacy outcomes in both trials is shown in Table 1:

Table 1. Efficacy at Week 24 in Patients 12 Years and Older with Cystic Fibrosis with a F508del or Other Responsive Mutation in the CFTR Gene

Primary Endpoint	*Trial 1 (N=398)*		*Trial 2 (N=573)*	
	Van/Tez/Deut	Elx/Tez/Iva	Van/Tez/Deut	Elx/Tez/Iva
Absolute change from baseline in ppFEV1 (percentage points)	0.5 (0.3)	0.3 (0.3)	0.2 (0.3)	0.0 (0.2)
LS Mean Difference (95% CI)*	*0.2 (-0.7 to 1.1)*		*0.2 (-0.5 to 0.9)*	
Key Secondary Endpoint				
Absolute change from baseline in SwCl (mmol/L)	-7.5 (0.8)	0.9 (0.8)	-5.1 (0.7)	-2.3 (0.7)
LS Mean Difference (95% CI)	*-8.4 (-10.5 to -6.3)*		*-2.8 (-4.7 to -0.9)*	

**The prespecified noninferiority margin was -3.0 percentage points.*

Key: CFTR, cystic fibrosis transmembrane conductance regulator; ppFEV1, percent predicted Forced Expiratory Volume in 1 second; Van/Tez/Deut, vanzacaftor/tezacaftor/deutivacaftor; Elx/Tez/Iva, elexacaftor/tezacaftor/ivacaftor

Most common adverse reactions to Van/Tex/Deut (≥5% of patients and at a frequency higher than Elx/Tez/Iva by ≥1%) were cough, nasopharyngitis, upper respiratory tract infection, headache, oropharyngeal pain, influenza, fatigue, increased ALT, rash, increased AST, and sinus congestion.

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 deutivacaftor-tezacaftor-vanzacaftor (Alyftrek) **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 deutivacaftor-tezacaftor-vanzacaftor per the FDA-approved label (Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7e635909-c6fd-4f0d-ae77-cdff03653a20 – see CLINICAL PHARMACOLOGY (12.1)) – laboratory documentation must be provided
3. Deutivacaftor-tezacaftor-vanzacaftor is not administered in combination with single-agent ivacaftor (Kalydeco), elexacaftor-tezacaftor-ivacaftor (Trikafta), lumacaftor/ivacaftor (Orkambi), or tezacaftor-ivacaftor co-packaged with ivacaftor (Symdeko)
4. Dose does not exceed two tablets of vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg daily with the following exception:
    a. Member is 6 to less than 12 years old AND weighs less than 40 kg: Three tablets of vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg daily
5. One of the following:
    a. Member is 6 years of age or older
    b. Member's age is within FDA approved labeling

Approval duration: 6 months

Continuation of deutivacaftor-tezacaftor-vanzacaftor (Alfytrek) **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 deutivacaftor-tezacaftor-vanzacaftor 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 deutivacaftor-tezacaftor-vanzacaftor **AND** has been receiving treatment with an ivacaftor-based regimen (Symdeko, Kalydeco, Orkambi, Trikafta) for a minimum of 18 months

3. Deutivacaftor-tezacaftor-vanzacaftor is not administered in combination with single-agent ivacaftor (Kalydeco), elexacaftor-tezacaftor-ivacaftor (Trikafta), lumacaftor/ivacaftor (Orkambi), or tezacaftor-ivacaftor co-packaged with ivacaftor (Symdeko)
4. Dose does not exceed two tablets of vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg daily with the following exception:
    a. Member is 6 to less than 12 years old AND weighs less than 40 kg: Three tablets of vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg daily
5. One of the following:
    a. Member is 6 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:

- Tablets:
    - Fixed-dose combination containing vanzacaftor 4 mg, tezacaftor 20 mg, and deutivacaftor 50 mg
    - Fixed-dose combination containing vanzacaftor 10 mg, tezacaftor 50 mg, and deutivacaftor 125 mg
- 6 to less than 12 years old:
    - Less than 40 kg: Three tablets of vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg (total dose of vanzacaftor 12 mg/tezacaftor 60 mg/ deutivacaftor 150 mg) daily

    - Greater than or equal to 40 kg: Two tablets of vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg (total dose of vanzacaftor 20 mg/tezacaftor 100 mg/ deutivacaftor 250 mg) daily

- 12 years and older: Two tablets of vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg (total dose of vanzacaftor 20 mg/tezacaftor 100 mg/ deutivacaftor 250 mg) daily

PRECAUTIONS:

- Drug-Induced Liver Injury and Liver Failure: Elevated transaminases have been observed in patients treated with ALYFTREK. Cases of serious and potentially fatal drug-induced liver injury and liver failure have been reported with a drug that contains the same or similar active ingredients as ALYFTREK. Assess liver function tests (ALT, AST, alkaline phosphatase, and bilirubin) in all patients prior to initiating and throughout treatment with ALYFTREK. Interrupt ALYFTREK in the event of significant elevations in liver function tests or signs or symptoms of liver injury. ALYFTREK should not be used in patients with severe hepatic impairment (Child-Pugh Class C). ALYFTREK is not recommended in patients with moderate hepatic impairment (Child-Pugh Class B).

- Hypersensitivity Reactions: Hypersensitivity reactions, including anaphylaxis, have been reported in the postmarketing setting for drugs containing elexacaftor, tezacaftor, and/or ivacaftor. If signs or symptoms of serious hypersensitivity reactions develop during ALYFTREK treatment, discontinue ALYFTREK and initiate appropriate therapy.

- Patients Who Discontinued or Interrupted Elexacaftor-, Tezacaftor-, or Ivacaftor-Containing Drugs Due to Adverse Reactions: Consider benefits and risks before using ALYFTREK in patients who discontinued or interrupted elexacaftor-, tezacaftor-, or ivacaftor-containing drugs due to adverse reactions. If ALYFTREK is used, closely monitor for adverse reactions as clinically appropriate.

- Reduced Effectiveness in Patients with Concomitant Use with CYP3A Inducers: Concomitant use with strong and moderate CYP3A inducers decreased vanzacaftor, tezacaftor, and deutivacaftor exposure, which may reduce ALYFTREK efficacy. Therefore, concomitant use is not recommended.

- Adverse Reactions with Concomitant Use with CYP3A Inhibitors: Concomitant use with strong or moderate CYP3A inhibitors increased vanzacaftor, tezacaftor, and deutivacaftor exposure, which may increase the risk of ALYFTREK associated adverse reactions. Reduce the ALYFTREK dosage with concomitant use.

- Cataracts: Non-congenital lens opacities/cataracts have been reported in patients with CF aged 18 years or less treated with drugs containing ivacaftor. Baseline and follow up ophthalmological examinations are recommended in pediatric patients.

BILLING/CODING INFORMATION:

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.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

None

RELATED GUIDELINES:

Genetic Testing, 05-82000-28

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

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

OTHER:

None

REFERENCES:

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2. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29 - [cited 2/1/25]. Available from: http://clinicaltrials.gov/.
3. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2/1/25].
4. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2025 [cited 2/1/25]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.
5. Vertex Pharmaceuticals. Symdeko (tezacaftor and ivacaftor) tablet. 2025 [cited 2/1/25]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7e635909-c6fd-4f0d-ae77-cdff03653a20 /.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 2/12/25.

GUIDELINE UPDATE INFORMATION:

04/01/25	New Medical Coverage Guideline.