09-J2000-97

Original Effective Date: 06/15/18

Reviewed: 04/10/24

Revised: 05/15/24

Subject: Tezacaftor/Ivacaftor (Symdeko)

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.

Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Tezacaftor and ivacaftor combination therapy was approved by the U.S. Food and Drug Administration (FDA) in 2018 for use in patients aged 12 years and older with cystic fibrosis (CF) who are homozygous for the F508 del mutation in the CF transmembrane conductance regulator (CFTR) gene or have at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor. This approval was expanded to include children 6 to 12 years of age in July 2019.

Tezacaftor/ivacaftor increases 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. Tezacaftor facilitates 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 tezacaftor/ivacaftor in patients with CF who are homozygous for the F508del mutation in the CFTR gene were evaluated in a randomized, double-blind, placebo-controlled, 24-week clinical trial in 504 patients. Treatment consisted of fixed-dose combination tezacaftor 100 mg/ivacaftor 150 mg orally in the morning and ivacaftor 150 mg orally in the evening or matching placebo. The placebo-adjusted absolute change from baseline in percentage of predicted FEV1 was a significant 4 percentage points in favor of tezacaftor/ivacaftor treatment (mean absolute change, +3.4 vs -0.6

percentage points, respectively). Also significantly improved with tezacaftor/ivacaftor versus placebo were the number of pulmonary exacerbations (estimated event rate, 0.64 vs 0.99 per year). Body mass index was not significantly different between groups at week 24. Discontinuation due to adverse events was 2.8% with active treatment and 3.1% with placebo. Overall, adverse event rates were similar between groups.

The efficacy and safety of tezacaftor/ivacaftor in patients with CF who are heterozygous for the F508del mutation but with a second allele with a CFTR mutation with residual function were evaluated in a randomized, double-blind, placebo-controlled, 8-week crossover trial in 248 patients.

Each patient received 2 of the following 3 treatment regimens in a crossover format that included 2 intervention periods of 8 weeks of active treatment followed by an 8-week washout period: (1) tezacaftor 100 mg orally once daily and ivacaftor 150 mg orally every 12 hours (combination therapy), (2) ivacaftor 150 mg orally every 12 hours (monotherapy), or (3) placebo. The mean difference versus placebo in absolute change in percentage of predicted FEV1 from baseline to the average of the week 4 and week 8 scores was significant for combination tezacaftor/ivacaftor (6.8 percentage points) and ivacaftor monotherapy (4.7 percentage points). The mean difference was also significant in favor of combination therapy versus monotherapy. The mean placebo-adjusted difference in absolute change from baseline to average of week 4 and week 8 in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score was also significant for the combination therapy (11.1 points) and monotherapy (9.7 points), but there was no significant difference between the 2 active treatment groups. A clinically important difference of 4 points or greater in the CFQ-R respiratory domain score occurred in 65% of the combination therapy group, 58% of the monotherapy group, and in 33% of the placebo group. Rates of adverse events were similar across groups.

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 tezacaftor/ivacaftor co-packaged with ivacaftor (Symdeko™) **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 a homozygous 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 tezacaftor/ivacaftor per the FDA-approved label (Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=302ae804-37db-44fd-ac2f-

3dbdeda9aa4b – see CLINICAL PHARMACOLOGY (12.1)) – laboratory documentation must be provided

3. Tezacaftor-ivacaftor co-packaged with ivacaftor is not administered in combination with single-agent ivacaftor (Kalydeco), elexacaftor-tezacaftor-ivacaftor (Trikafta), or lumacaftor/ivacaftor (Orkambi)
4. Dose does not exceed two tablets per day
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 tezacaftor/ivacaftor co-packaged with ivacaftor (Symdeko™) **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 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. Tezacaftor-ivacaftor co-packaged with ivacaftor is not administered in combination with single-agent ivacaftor (Kalydeco), elexacaftor-tezacaftor-ivacaftor (Trikafta), or lumacaftor/ivacaftor (Orkambi)
4. Dose does not exceed two tablets per day
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:

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

- Pediatric patients age 6 to less than 12 years weighing less than 30 kg: one tablet (containing tezacaftor 50 mg/ivacaftor 75 mg) in the morning and one tablet (containing ivacaftor 75 mg) in the evening, approximately 12 hours apart
- Adults and pediatric patients ages 12 years and older: one tablet (containing tezacaftor 100 mg/ivacaftor 150 mg) in the morning and one tablet (containing ivacaftor 150 mg) in the evening, approximately 12 hours apart
- Take with fat-containing food

Dose Adjustments

- Reduce dose in patients with moderate and severe hepatic impairment
- Reduce dose when co-administered with drugs that are moderate or strong CYP3A inhibitors

Drug Availability

- Co-packaged as tezacaftor 100 mg/ivacaftor 150 mg fixed dose combination tablets and ivacaftor 150 mg tablets
- Co-packaged as tezacaftor 50 mg/ivacaftor 75 mg fixed-dose combination tablets and ivacaftor 75 mg tablets

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- Elevated transaminases (ALT or AST)
- Use with CYP3A4 inducers
- Cataracts

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

OTHER:

None

REFERENCES:

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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. 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/.
5. Vertex Pharmaceuticals. Symdeko (tezacaftor and ivacaftor) tablet. 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=302ae804-37db-44fd-ac2f-3dbdeda9aa4b#S12.1/.

COMMITTEE APPROVAL:

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

GUIDELINE UPDATE INFORMATION:

06/15/18	New Medical Coverage Guideline.
05/15/19	Review and revision to guideline; consisting of updating references.
08/15/19	Revision to guideline description, position statement, dosing, references
04/14/21	Review and revision to guideline; consisting of updating position statement and references.
05/15/21	Review and revision to guideline; consisting of updating position statement and references.
07/15/21	Revision to position statement
05/15/24	Review and revision to guideline; consisting of updating references.