09-J2000-29

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Reviewed: 04/14/21

Revised: 05/15/21

Next Review: 04/13/22

Subject: Lumacaftor/Ivacaftor (Orkambi™) Capsule

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:

Lumacaftor and ivacaftor combination therapy was approved by the U.S. Food and Drug Administration (FDA) in July 2015 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. The approval was expanded to included children 6 years and older in September 2016 and to include those 2 years and older in August 2018. In the US, this mutation represents approximately 8,500 patients with CF (half of the total CF population). There is currently no treatment available that specifically targets this particular mutation; current treatment options only address complications associated with the disease. Prior to FDA approval, lumacaftor/ivacaftor was designated as an Orphan Drug for its FDA-approved indication.

Lumacaftor is a CFTR corrector and ivacaftor is a CFTR potentiator. The efficacy of lumacaftor/ivacaftor in patients with CF who are homozygous for the F508del mutation in the CFTR gene was evaluated in two randomized, double-blind, placebo-controlled, 24-week clinical trials (Trials 1 and 2) in 1108 clinically stable patients with CF of whom 369 patients received lumacaftor/ivacaftor twice daily.

Trial 1 evaluated 549 patients with CF who were aged 12 years and older (mean age 25.1 years) with ppFEV1 at screening between 40-90 [mean ppFEV1 60.7 at baseline (range: 31.1 to 94.0)]. Trial 2 evaluated 559 patients aged 12 years and older (mean age 25.0 years) with ppFEV1 at screening between 40-90 [mean ppFEV1 60.5 at baseline (range: 31.3 to 99.8)].

Patients in both trials were randomized 1:1:1 to receive either lumacaftor 400 mg q12h/ivacaftor 250 mg q12h; or lumacaftor 600 mg once daily/ivacaftor 250 mg q12h or placebo. Patients took the study drug

with fat-containing food for 24 weeks in addition to their prescribed CF therapies (e.g., bronchodilators, inhaled antibiotics, dornase alfa, and hypertonic saline).

The primary efficacy endpoint in both trials was change in lung function as determined by absolute change from baseline in ppFEV1 at Week 24, assessed as the average of the treatment effects at Week 16 and at Week 24. In both trials, treatment with lumacaftor/ivacaftor resulted in a statistically significant improvement in ppFEV1. The treatment difference between lumacaftor/ivacaftor and placebo for the mean absolute change in ppFEV1 from baseline at Week 24 (assessed as the average of the treatment effects at Week 16 and at Week 24) was 2.6 percentage points [95% CI (1.2, 4.0)] in Trial 1 (P=0.0003) and 3.0 percentage points [95% CI (1.6, 4.4)] in Trial 2 (P<0.0001). These changes persisted throughout the 24-week treatment period (Figure 1). Improvements in ppFEV1 were observed regardless of age, disease severity, sex, and geographic region.

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration 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 lumacaftor/ivacaftor (Orkambi™) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member is diagnosed with cystic fibrosis (CF)
2. 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
3. Lumacaftor-ivacaftor is not administered in combination with single-agent ivacaftor (Kalydeco), elexacaftor-tezacaftor-ivacaftor (Trikafta), or co-packaged tezacaftor/ivacaftor (Symdeko)
4. Dose does not exceed:
    a. Adults and children 12 years of age and older: Two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) twice daily
    b. Children 6 through 11 years of age: Two tablets (each containing lumacaftor 100 mg/ivacaftor 125 mg) twice daily
    c. Children 2 through 5 years of age:
        i. Body weight less than 14 kg: one packet (each containing lumacaftor 100 mg/ivacaftor 125 mg) twice daily
        ii. Body weight 14 kg or greater: one packet (each containing lumacaftor 150 mg/ivacaftor 188 mg) twice daily
5. Member is 2 years of age or older

Approval duration: 6 months

Continuation of lumacaftor/ivacaftor (Orkambi™) **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 lumacaftor/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 lumacaftor/ivacaftor **AND** has been receiving treatment for a minimum of 18 months
3. Lumacaftor-ivacaftor is not administered in combination with single-agent ivacaftor (Kalydeco), elexacaftor-tezacaftor-ivacaftor (Trikafta), or co-packaged tezacaftor/ivacaftor (Symdeko)
4. Dose does not exceed:
    a. Adults and children 12 years of age and older: Two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) twice daily
    b. Children 6 through 11 years of age: Two tablets (each containing lumacaftor 100 mg/ivacaftor 125 mg) twice daily
    c. Children 2 through 5 years of age:
        i. Body weight less than 14 kg: one packet (each containing lumacaftor 100 mg/ivacaftor 125 mg) twice daily
        ii. Body weight 14 kg or greater: one packet (each containing lumacaftor 150 mg/ivacaftor 188 mg) twice daily
5. Member is 2 years of age or older

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

- Age 12 years and older: Two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) taken orally every 12 hours

- Age 6 through 11 years: Two tablets (each containing lumacaftor 100 mg/ivacaftor 125 mg) taken orally every 12 hours
- Children 2 through 5 years of age:
    - Body weight less than 14 kg: one packet (each containing lumacaftor 100 mg/ivacaftor 125 mg) twice daily
    - Body weight 14 kg or greater: one packet (each containing lumacaftor 150 mg/ivacaftor 188 mg) twice daily

Dose Adjustments

- Reduce dose in patients with moderate or severe hepatic impairment
- Reduce dose for the first week of treatment in patients taking strongCYP3A inhibitors

Drug Availability

- Tablets: lumacaftor 100 mg and ivacaftor 125 mg; lumacaftor 200 mg and ivacaftor 125 mg
- Oral granules: Unit-dose packets of lumacaftor 100 mg and ivacaftor 125 mg; lumacaftor 150 mg and ivacaftor 188 mg

PRECAUTIONS

Contraindications

None

Precautions/Warnings

- Liver-related events: Elevated transaminases (ALT/AST) have been observed in some cases associated with elevated bilirubin
- Respiratory events: Chest discomfort, dyspnea, and respiration abnormal were observed more commonly during initiation
- Drug interactions: Use with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index may decrease systemic exposure of the medicinal products and co-administration is not recommended

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 revised date.

DEFINITIONS:

None

RELATED GUIDELINES:

Genetic Testing, 05-82000-28

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

OTHER:

None

REFERENCES:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 4/14/21.

GUIDELINE UPDATE INFORMATION:

03/15/15	New Medical Coverage Guideline.
09/15/15	Revision to guideline; consisting of position statement, dosage/administration.
11/01/15	Revision: ICD-9 Codes deleted.
03/15/16	Review and revision; consisting of updating position statement.
04/15/16	Revision to guideline; consisting of updating position statement.
11/15/16	Revision to guideline; consisting of updating position statement, dosage/administration, description
03/15/17	Revision to guideline; consisting of updating position statement.
06/15/17	Review and revision to guideline; consisting of updating references.
5/15/18	Review and revision to guideline; consisting of updating references.
11/15/18	Revision to guideline; consisting of updating position statement and dosing.
05/15/19	Review and revision to guideline; consisting of updating position statement and references.
05/15/20	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.