Effective Date **7/15/2024**
Coverage Policy Number **IP0432**

Lumacaftor/Ivacaftor

Table of Contents

Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for lumacaftor/ivacaftor (**Orkambi®**).

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Lumacaftor/ivacaftor (Orkambi) is considered medically necessary when the following are met:

1. **Cystic Fibrosis (CF).** Individual meets **ALL** of the following criteria (A, B, C, D, E and F):
   A. Patient is 1 year of age or older
   B. Patient meets at least ONE of the following (i, ii, or iii):
      i. Positive cystic fibrosis newborn screening test; OR
      ii. Family history of cystic fibrosis; OR
      iii. Clinical presentation consistent with signs and symptoms of cystic fibrosis; AND
      Note: Examples of clinical presentation of cystic fibrosis include but are not limited to meconium ileus, sino-pulmonary symptoms (e.g., persistent cough, wheezing, pulmonary

function tests consistent with obstructive airway disease, excess sputum production), bronchiectasis, sinusitis, failure to thrive, pancreatic insufficiency.

C. Patient has TWO copies of the F508del mutation in the CFTR gene
D. Patient has evidence of abnormal cystic fibrosis transmembrane conductance regulator function as demonstrated by at least ONE of the following (i, ii, or iii):
    i. Elevated sweat chloride test; OR
    ii. Two cystic fibrosis-causing cystic fibrosis transmembrane conductance regulator mutations; OR
    iii. Abnormal nasal potential difference; AND
E. The medication is prescribed by, or in consultation with, a pulmonologist or a physician who specializes in the treatment of cystic fibrosis
F. Patient meets the preferred covered alternative(s) criteria as indicated in the table below [Cigna Total Savings]

Coverage varies across plans and requires the use of preferred products. Refer to the customer's benefit plan document for coverage details.

Employer Group Non-Covered Products and the Preferred Covered Alternatives:

Non-Covered Product	Criteria
Orkambi (lumacaftor/ivacaftor tablets and oral granules)	**Cigna Total Savings Drug List Plans:** There is documentation of **ONE** of the following (A, B, or C): A. The individual has had an inadequate response, contraindication, or is intolerant to elexacaftor/tezacaftor/ivacaftor (Trikafta™) B. Individual is less than 6 years of age C. Individual has previously been started on, or is currently receiving Orkambi

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Lumacaftor/ivacaftor (Orkambi) is considered medically necessary for continued use when initial criteria are met AND there is documentation of beneficial response.

Examples of beneficial response include:

For individuals who already have measureable lung disease or end organ involvement: there is improvement in, stabilization of, or a decrease in the rate of decline of FEV1; reduced number of pulmonary exacerbations; improvement in body mass index (BMI); or improvement on the patient reported Cystic Fibrosis Questionnaire-Revised respiratory domain score

For individuals who are previously asymptomatic, or have mild clinical manifestations: there is no evidence of clinical decline

Authorization Duration

Initial approval duration: up to 12 months
Reauthorization approval duration: up to 12 months

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

1. **Cystic Fibrosis, Heterozygous for the F508del (Phe508del) Mutation in the CFTR Gene.** Orkambi is not indicated for patients with only one copy of the F508del mutation in the CFTR gene.[1]

2. **Combination Therapy with Kalydeco® (ivacaftor tablets and oral granules), Symdeko® (tezacaftor/ivacaftor; ivacaftor tablets, co-packaged), or Trikafta® (elexacaftor/tezacaftor/ivacaftor tablets; ivacaftor tablets, co-packaged).** Orkambi contains ivacaftor, the active agent in Kalydeco and therefore is not indicated in combination with Kalydeco. Symdeko and Trikafta contain ivacaftor and are therefore not indicated in combination with Orkambi.

3. **Infertility.** Orkambi is indicated for the treatment of cystic fibrosis in a patient ≥ 1 year of age who is homozygous for the F508del mutation in the cystic fibrosis transmembrane regulator (CFTR) gene.[1] Note: A patient with a diagnosis of cystic fibrosis should be reviewed using criteria for the FDA-approved indication, above.

Background

OVERVIEW

Orkambi, a combination of lumacaftor and ivacaftor, is indicated for the treatment of **cystic fibrosis** in patients ≥ 1 year of age who are homozygous for the F508del mutation in the cystic fibrosis transmembrane regulator (CFTR) gene.[1]

If the patient's genotype is unknown, an FDA-cleared cystic fibrosis mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene. The efficacy and safety of Orkambi have not been established in patients with cystic fibrosis other than those homozygous for the F508del mutation. Orkambi contains a unique chemical entity, lumacaftor, which is a CFTR corrector that increases trafficking of F508del CFTR to the cell surface, and ivacaftor (the same active ingredient contained in Kalydeco® [ivacaftor tablets and oral granules]), a CFTR potentiator that enhances chloride transport of CFTR on the cell surface. The F508del mutation in CFTR causes cystic fibrosis by limiting the amount of CFTR protein that reaches the epithelial cell surface.

Guidelines

According to the CF Foundation (2017), CF is diagnosed when an individual has both a clinical presentation of CF and evidence of CFTR dysfunction.[2,3] Clinical presentation of CF includes a positive newborn screening, signs and/or symptoms of CF, and/or family history of CF. To establish a diagnosis of CF, sweat chloride tests should be considered first, then CFTR genetic analysis (CFTR genotype), and then CFTR physiologic tests (nasal potential difference [NPD] or intestinal current measurement [ICM]). However, tests of CFTR function are not always done in this order. All individuals diagnosed with CF should have a sweat chloride test and CFTR genetic analysis performed.

In a patient with a sweat chloride test ≥ 60 mmol/L, CF diagnosis is established and in patients with a sweat chloride test < 30 mmol/L, a diagnosis of CF is unlikely.[2,3] Rarely, patients with a sweat chloride < 30 mmol/L may be considered to have CF if alternatives are excluded and other confirmatory tests (genetic and physiologic testing) support CF. In patients with a sweat chloride test of ≥ 30 to < 60 mmol/L, CFTR genetic analysis is undertaken. If the genetic analysis identifies two CF-causing CFTR mutations, CF is diagnosed, if no CFTR mutations are identified, a diagnosis of CF is unlikely. In patients with a CFTR genotype that is undefined or of varying clinical consequence, full gene CFTR sequencing (if not already performed) or CFTR physiologic testing is performed (NPD or ICM). If only one CFTR variant is identified on limited analysis, full gene CFTR

sequencing be performed. CF is possible if both alleles posses CF-causing, undefined, or mutation of varying clinical consequence mutations; CF is unlikely if only no CF-causing mutations are found. If results of the NPD or ICM show CFTR dysfunction, CF is diagnosed; when testing is unavailable or equivocal, the diagnosis of CF is not resolved, and when results of the physiologic testing show CFTR function is preserved, a diagnosis of CF is considered unlikely. It is recommended that patients with challenging diagnoses be evaluated at an accredited CF Foundation Care Center.

References

1. Orkambi® tablets and oral granules [prescribing information]. Cambridge, MA: Vertex; September 2022.
2. Farrell PM, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: consensus guidelines from the cystic fibrosis foundation. *J Pediatr*. 2017;181S:S4-S15.
3. Farrell PM, White TB, Howenstine MS, et al. Diagnosis of cystic fibrosis in screened populations. *J Pediatr.* 2017;181S:S33-S44.