Drug Coverage Policy

Effective Date……9/1/2025
Coverage Policy Number……IP0432
Policy Title……Orkambi

Cystic Fibrosis Transmembrane Conductance Regulator – Orkambi

- Orkambi® (lumacaftor/ivacaftor tablets and oral granules – Vertex)

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. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. 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

Orkambi, a combination of lumacaftor and ivacaftor, is indicated for the treatment of **cystic fibrosis (CF)** in patients ≥ 1 year of age who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance 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

The most current treatment recommendations are the Standards of Care for CFTR variant-specific therapy for people with CF, from the European Cystic Fibrosis Society (2023).[4] However, the Standards do not reflect the currently approved age indications for Kalydeco® (ivacaftor tablets and oral granules) [≥ 1 months of age], Orkambi (≥ 1 year of age), or Trikafta® (elexacaftor/tezacaftor/ivacaftor; ivacaftor co-packaged tablets and granules) [≥ 2 years of age]. In general, Trikafta is recommended over other agents where indications overlap. The Standards recommend Trikafta in patients ≥ 6 years of age with CF who are homozygous or heterozygous for F508del. In patients with one or more responsive non-F508del variant, Kalydeco, Symdeko® (tezacaftor/ivacaftor tablets; ivacaftor tablets), or Trikafta are recommended. Kalydeco is recommended in patients ≥ 4 months of age with eligible CFTR gene variants. Orkambi is recommended for patients 2 to 5 years of age who are homozygous for F508del. Of note, the Standards state that after diagnosis, repeat sweat testing provides evidence of treatment effect on CFTR activity, but does not predict clinical response. The European Cystic Fibrosis Society Standards for establishing and maintaining health (2024) note that people with CF with eligible CFTR gene variants should be offered CFTR modulator therapy.[4]

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 should be performed. CF is possible if both alleles possess 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.

Coverage Policy

POLICY STATEMENT
Prior Authorization is required for benefit coverage of Orkambi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Orkambi as well as the monitoring required for adverse events and long-term efficacy, approval requires Orkambi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but not limited to, chart notes, laboratory tests, medical test results, claims records, and/or other information.

Orkambi is considered medically necessary when the following criteria are met:

FDA-Approved Indication

1. **Cystic Fibrosis, Homozygous for the F508del Mutation in the Cystic Fibrosis Transmembrane Conductance Regulator Gene.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, E and F):
   - **A)** Patient is ≥ 1 year of age; AND
   - **B)** Patient has TWO copies of the F508del mutation in the cystic fibrosis transmembrane conductance regulator gene **[documentation required]**; AND
   - **C)** 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.
   - **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; AND
   - **F)** Preferred product criteria is met for the products listed in the below table

Employer Plans:

Product	Criteria
Orkambi (lumacaftor/ivacaftor tablets and oral granules)	**Total Savings Drug List Plans:** **ONE** of the following: 1. Patient is ≥ 2 years AND the patient has tried, and according to the prescriber has experienced inadequate efficacy OR a significant intolerance with Trikafta (tablets or oral granules) [may require prior authorization] 2. Patient is < 2 years of age 3. Patient has already been started on therapy with 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.

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

Conditions Not Covered

Orkambi for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Cystic Fibrosis, Heterozygous for the F508del Mutation in the Cystic Fibrosis Transmembrane Conductance Regulator Gene.** Orkambi is not indicated for a patient with only one copy of the F508del mutation in the CFTR gene.[1]

2. **Combination Therapy with Other Cystic Fibrosis Transmembrane Conductance Regulator Modulator(s) .** Orkambi contains ivacaftor, the active agent in Kalydeco® (tablets and oral granules) and therefore is not indicated in combination with Kalydeco. Symdeko® (tezacaftor/ivacaftor tablets; ivacaftor tablets) and Trikafta® (elexacaftor/tezacaftor/ivacaftor; ivacaftor co-packaged tablets and granules) contain ivacaftor and are therefore not indicated in combination with Orkambi.
   Note: Examples of other cystic fibrosis transmembrane conductance regulator modulators are: Alyftrek™ (vanzacaftor/tezacaftor/deutivacaftor tablets), Kalydeco (ivacaftor tablets and oral granules), Symdeko (tezacaftor/ivacaftor; ivacaftor tablets), Trikafta (elexacaftor/tezacaftor/ivacaftor; ivacaftor co-packaged tablets and granules).

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.

References

1. Orkambi® tablets and oral granules [prescribing information]. Cambridge, MA: Vertex; December 2024.
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.
4. Southern KW, Addy C, Bell SC, et al. Standards for the care of people with cystic fibrosis; establishing and maintaining health. *J Cyst Fibros.* 2024;21-28.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	**Preferred Covered Alternative Table.** **Updated** 'inadequate response' to 'failure'	10/15/2024

	Updated 'Individual is less than 6 years of age' to 'Individual is less than 2 years of age'	
Selected Revision	The Policy title was changed to Cystic Fibrosis Transmembrane Conductance Regulator – Orkambi. Previously, Cystic Fibrosis – Orkambi. **Added "<u>Documentation</u>:** Documentation is required where noted in the criteria. Documentation may include, but not limited to, chart notes, laboratory tests, medical test results, claims records, and/or other information." **Cystic Fibrosis Homozygous for the F508del Mutation in the Cystic Fibrosis Transmembrane Conductance Regulator Gene**. "Conductance" was added to this criteria. **Updated** criteria **from** "Patient has TWO copies of the F508del mutation in the CFTR gene" **to** "Documentation is provided that the patient has TWO copies of the F508del mutation in the cystic fibrosis transmembrane conductance regulator gene." **Cystic Fibrosis, Heterozygous for the F508del Mutation in the Cystic Fibrosis Transmembrane Conductance Regulator Gene Mutation.** "Conductance" was added to the verbiage for this condition not covered. **Combination Therapy with Other Cystic Fibrosis Transmembrane Conductance Regulator Modulator(s).** This condition not covered was modified to refer to the class of cystic fibrosis transmembrane conductance regulator modulator(s). Previously individual agents were listed. A Note was added to list examples of the cystic fibrosis transmembrane conductance regulators. **Preferred Product Table:** **Updated from** "Failure, contraindication, or intolerance with to Trikafta" **to** "Patient is ≥ 2 years AND the patient has tried, and according to the prescriber has experienced inadequate efficacy OR a significant intolerance with Trikafta (tablets or oral granules) [may require prior authorization]." **Updated from** "Patient is < 2 years of age, approve" **to** "Patient is < 2 years of age." **Updated from** "If the patient has been started on Orkambi, approve" **to** "Patient has already been started on therapy with Orkambi."	4/1/2025
Annual Revision	No criteria changes	9/1/2025

The policy effective date is in force until updated or retired.