Effective Date **12/1/2023**
Next Review Date… **12/1/2024**
Coverage Policy Number **IP0432**

Lumacaftor/Ivacaftor

Table of Contents

Related Coverage Resources

Genetic Testing for Hereditary and Multifactorial Conditions
Pharmacogenetic Testing

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, and E):
   A. Individual is 1 year of age or older
   B. Documented diagnosis of cystic fibrosis (CF) [i.e., a clinical presentation consistent with signs/symptoms of CF, a positive CF newborn screening test, or family history of CF AND evidence of abnormal CFTR function (as demonstrated by elevated sweat chloride, detection of two CF-causing CFTR mutations, or abnormal nasal potential differences)] [Appendix]

C. Documentation the individual is homozygous for the F508del variant in the CFTR gene (i.e., 2 copies of the F508del variant)
D. The medication is prescribed by, or in consultation with, a pulmonologist or a physician who specializes in the treatment of cystic fibrosis
E. Individual meets the preferred covered alternative(s) criteria as indicated in the table below [Cigna Total Savings and Individual and Family Plans]

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

Individual and Family Plans Non-Covered Products and the Preferred Covered Alternatives:

Non-Covered Product	Criteria
Orkambi (lumacaftor/ivacaftor tablets and oral granules)	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. **Cystic Fibrosis (CF), Patients with Unknown Cystic Fibrosis Transmembrane Regulator (CFTR) Gene Mutation.** An FDA-cleared CF mutation test should be used to detect the presence of the CFTR mutation prior to use of Orkambi[1]

3. **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.

4. **CFTR-related disorder (for example, congenital absence of the vas deferens (CAVD), isolated pancreatitis, recurrent sinusitis or bronchitis).**

5. **CFTR-related metabolic syndrome, CF Screen Positive, Inconclusive Diagnosis (CRMS/CFSPID).**

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.

Appendix

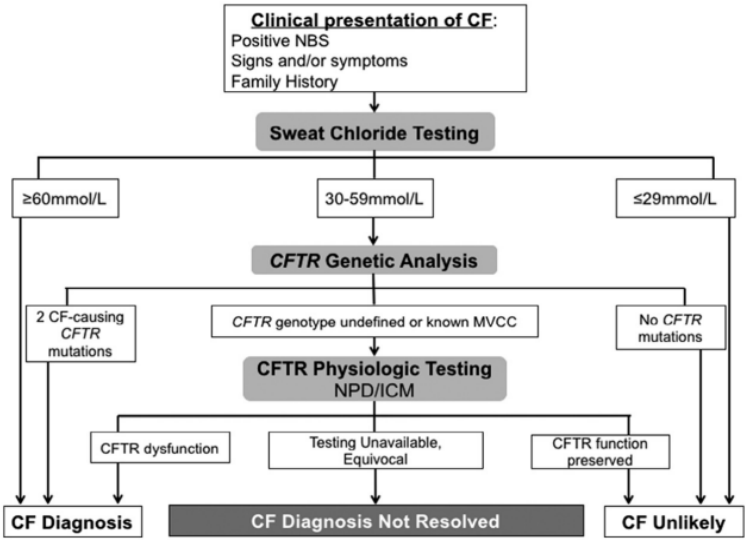

Figure. CF is diagnosed when an individual has both a clinical presentation of the disease and evidence of CFTR dysfunction. The tests of CFTR function are not always done in this order, but hierarchically to establish the diagnosis of CF, sweat chloride should be considered first, then *CFTR* genetic analysis, and then CFTR physiologic tests. All individuals diagnosed with CF should have a sweat test and a *CFTR* genetic analysis performed. Rare individuals with a sweat chloride <30 mmol/L may be considered to have CF if alternatives are excluded and the other confirmatory tests (genetic, physiologic testing) support CF. If only 1 *CFTR* variant is identified on limited analysis, further ("extended") *CFTR* testing should be performed.[22] CF is possible if both alleles possess CF-causing, undefined, or mutation of varying clinical consequence (MVCC) mutations; CF is unlikely if only non-CF-causing mutations are found. If a CF diagnosis is not resolved, CRMS/CFSPID (following NBS) or CFTR-related disorder should be considered.[9,29] Rarely, no distinct label may be appropriate but further follow-up may be warranted. In these cases, the use of "CF carrier" or the specific clinical problem should be used for characterization/labeling purposes.

NBS – newborn screen, NPD – nasal potential difference, ICM – intestinal current measurement
Farrell PM, White TB, Ren CL, et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. J Pediatr 2017; 181S:S4.[3]

References

1. Orkambi® tablets and oral granules [prescribing information]. Cambridge, MA: Vertex; September 2022.
2. Ren CL, Morgan RL, Oermann C, et al. Cystic Fibrosis Foundation Pulmonary Guidelines: Use of cystic fibrosis transmembrane conductance regulator modulator therapy in patients with cystic fibrosis. *Ann Am Thorac Soc*. 2018;15(3):271-280.
3. Farrell PM, White TB, Ren CL, et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. J Pediatr 2017; 181S:S4.