PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis Transmembrane Conductance Regulator – Orkambi Prior Authorization Policy

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

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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.5

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.

Policy Statement

Prior Authorization is recommended for prescription 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.

Automation: None.

Recommended Authorization Criteria

Coverage of Orkambi is recommended in those who meet the following criteria:

FDA-Approved Indication

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, and E):

Patient is ≥ 1 year of age; AND

Patient has TWO copies of the F508del mutation in the cystic fibrosis transmembrane conductance regulator gene; AND

Patient meets at least ONE of the following (i, ii, or iii):

Positive cystic fibrosis newborn screening test; OR

Family of cystic fibrosis; OR

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.

Patient has evidence of abnormal cystic fibrosis transmembrane conductance regulator function as demonstrated by at least ONE of the following (i, ii, or iii):

Elevated sweat chloride test; OR

Two cystic fibrosis-causing cystic fibrosis transmembrane conductance regulator mutations; OR

Abnormal nasal potential difference; AND

The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

Conditions Not Recommended for Approval

Coverage of Orkambi is not recommended in the following situations:

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 cystic fibrosis transmembrane conductance regulator gene.1

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).

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 gene.1

Note: A patient with a diagnosis of cystic fibrosis should be reviewed using criteria for the FDA-approved indication, above.

Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

References

Orkambi® tablets and oral granules [prescribing information]. Cambridge, MA: Vertex; August 2023.

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