PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Orkambi Prior Authorization Policy
- Orkambi® (lumacaftor/ivacaftor tablets and oral granules – Vertex)

REVIEW DATE: 07/05/2023; selected revision 04/10/2024

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.

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

1. **Cystic Fibrosis, Homozygous for the F508del Mutation in the Cystic Fibrosis Transmembrane Regulator (CFTR) Gene.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 1 year of age; AND
   - **B)** Patient has TWO copies of the F508del mutation in the CFTR gene; AND
   - **C)** Patient meets at least ONE of the following (i, ii, or iii):
     - **i.** Positive cystic fibrosis newborn screening test; OR
     - **ii.** Family 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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Orkambi is not recommended in the following situations:

1. **Cystic Fibrosis, Heterozygous for the F508del Mutation in the CFTR 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 Kalydeco, Symdeko, or Trikafta.** 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.

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

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.