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Section:	Prescription Drugs	**Effective Date:**	October 1, 2024
Subsection:	Respiratory Agents	**Original Policy Date:**	July 17, 2015
Subject:	Orkambi	**Page:**	1 of 8

Last Review Date: September 6, 2024

Orkambi

Description

Orkambi (lumacaftor/ivacaftor)

Background
Orkambi (lumacaftor/ivacaftor) is used for the treatment of cystic fibrosis (CF) in patients who have two copies of the F*508del* mutation in their cystic fibrosis transmembrane conductance regulator (CFTR) gene. CF is a progressive disease that results in the formation of thick mucus that builds up in the lungs, digestive tract and other parts of the body leading to severe respiratory and digestive problems, as well as other complications such as infections and diabetes. The CFTR protein is a chloride channel present at the surface of epithelial cells in multiple organs. The *F508del* mutation results in protein misfolding, causing a defect in cellular processing and trafficking that targets the protein for degradation and therefore reduces the quantity of CFTR at the cell surface. The small amount of F508del-CFTR that reaches the cell surface is less stable and has low channel-open probability (defective gating activity) compared to wild-type CFTR protein. Lumacaftor improves the conformational stability of F508del-CFTR, resulting in increased processing and trafficking of mature protein to the cell surface. Ivacaftor is a CFTR potentiator that facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein at the cell surface (1-2).

Regulatory Status
FDA-approved indication: Orkambi is a combination of lumacaftor and ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, indicated for the treatment of cystic

fibrosis (CF) in patients aged 1 year and older who are homozygous for the *F508del* mutation in the *CFTR* gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the *F508del* mutation on both alleles of the *CFTR* gene (1).

Limitations of Use:
The efficacy and safety of Orkambi have not been established in patients with CF other than those homozygous for the *F508del* mutation. Orkambi should not be used in patients other than those who have two copies of the *F508del* mutation in their *CFTR* gene (1).

Orkambi may cause worsening of liver function, including hepatic encephalopathy, in patients with advanced liver disease and should be used with caution and only if the benefits are expected to outweigh the risks. If Orkambi is used in these patients, they should be closely monitored after the initiation of treatment and the dose should be reduced (1).

Transaminases (ALT or AST) should be assessed prior to initiating Orkambi, every 3 months during the first year of treatment, and annually thereafter. Patients who develop increased transaminase levels should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients with ALT or AST of greater than 5 times the upper limit of normal (1).

Respiratory events may be observed in patients during initiation of Orkambi. These events can be serious, particularly in patients with advanced lung disease. Clinical experience in patients with $ppFEV_1<40$ is limited, and additional monitoring of these patients is recommended during initiation of therapy (1).

Based on the clinical studies that were done for Orkambi, patients who had abnormal liver function (defined as any 3 or more of the following: ≥3 × upper limit of normal (ULN) aspartate aminotransferase (AST), ≥3 × ULN alanine aminotransferase (ALT), ≥3 × ULN gamma-glutamyl transpeptidase (GGT), ≥3 × ULN alkaline phosphatase (AP) or total bilirubin ≥2 × ULN) were not eligible for the study (1).

For newly diagnosed older adults, other cystic fibrosis options for *F508del* mutation should be considered due to the increased drug interactions, increases in blood pressure, and the risk of hepatic encephalopathy with Orkambi (1).

Orkambi has not studied in patients with mild, moderate, or severe renal impairment or in patients with end-stage renal disease. No dose adjustment is necessary for patients with mild to

moderate renal impairment. Caution is recommended while using Orkambi in patients with severe renal impairment (creatinine clearance ≤30 mL/min) or end-stage renal disease (1).

The safety and efficacy of Orkambi in patients less than 1 year of age have not been established (1).

Related policies
Kalydeco, Pulmozyme, Symdeko, Trikafta

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Orkambi may be considered **medically necessary** if the conditions indicated below are met.

Orkambi may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 1 year of age or older

Diagnosis

Patient must have the following:

Cystic fibrosis (CF)

AND ALL of the following:

1. Homozygous for *F508del* mutation in the cystic fibrosis transmembrane regulator (CFTR) gene confirmed by FDA approved CF mutation test
2. Patients 6 years of age or older **only**: pretreatment percent predicted forced expiratory volume (ppFEV1) must be provided
3. Patients 6 years of age or older **only:** inadequate treatment response, intolerance, or contraindication to Symdeko (tezacaftor/ivacaftor)
4. Baseline levels of ALT, AST, and bilirubin must not be greater than 3x the upper limit of normal
5. Must be prescribed by a pulmonologist, or gastroenterologist

6. **NO** dual therapy with another cystic fibrosis transmembrane conductance regulator (CFTR) potentiator (see Appendix 1)

Prior – Approval *Renewal* Requirements

Age 1 year of age or older

Diagnosis

Patient must have the following:

Cystic fibrosis (CF)

AND ALL of the following:

1. Patients less than 6 years of age **only**: Patient's symptoms have improved or stabilized from baseline
2. Patients 6 years of age or older **only**: Stable or improvement of ppFEV$_1$ from baseline
3. Annual testing of ALT, AST, and bilirubin levels after the first year of therapy
4. **NO** dual therapy with another cystic fibrosis transmembrane conductance regulator (CFTR) potentiator (see Appendix 1)

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Quantity 336 tablets per 84 days **OR**
168 packets per 84 days

Duration 6 months

Prior – Approval *Renewal* Limits

Quantity	336 tablets per 84 days **OR** 168 packets per 84 days
Duration	12 months

Rationale

Summary
Cystic fibrosis (CF) is caused by mutations in a gene that encodes for a protein called cystic fibrosis transmembrane regulator (CFTR) which regulates chloride and water transport in the body. The defect results in the formation of thick mucus that builds up in the lungs, digestive tract and other parts of the body. Orkambi (lumacaftor/ivacaftor) is a potentiator of the CFTR protein and is effective only in CF patients who are homozygous for the *F508del* mutation in the *CFTR* gene. Orkambi is not effective in patients who are not homozygous for the *F508del* mutation in the CFTR gene. Orkambi is indicated for patients 1 year of age and older (1-2).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of Orkambi while maintaining optimal therapeutic outcomes.

References

1. Orkambi [package insert]. Boston, MA: Vertex Pharmaceuticals Incorporated; August 2023.
2. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. N Engl J Med 2015; 373:220-23. DOI: 10.1056/NEJMoa1409547.

Policy History

Date	Action
July 2015	Addition to PA
July 2015	Removal of not to be used concurrently with other medications for cystic fibrosis and the addition of no dual therapy with another a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator

	Change of quantity limits from 360/ 90 days to 336/ 84 days due to packaging
September 2015	Annual Review Removal of baseline percent predicted forced expiratory volume (ppFEV1) of greater than or equal to (≥) 40 and addition of gastroenterologist
December 2015	Annual editorial review and reference update Addition of pretreatment percent predicted forced expiratory volume (ppFEV1) must be provided; patient has a hemoglobin must be greater than or equal to 10g/dL; patient has an eGFR must be greater than or equal to 50ml/min; absence of **ALL** of the following organisms: burkholeria cenocepacia, burkholderia dolosa, mycobacterium abscessus; absence of 2 respiratory cultures in past 12 months; baseline levels of ALT, AST and bilirubin must not be greater than 3x the upper limit of normal.
March 2016	Annual review Policy number changed from 5.13.06 to 5.45.06
September 2016	Annual editorial review and reference update. Added age to renewal criteria
October 2016	Change to new age of 6 yrs. and older
March 2017	Annual editorial review and reference update
March 2018	Annual review
June 2018	Annual editorial review and reference update Removal of requirement: patient has had 2 negative respiratory cultures for any of the following organisms: burkholeria cenocepacia, burkholderia dolosa, or mycobacterium abscessus in the past 12 months per SME
August 2018	Lowered age limit to patients 2 years and older, addition of packets to quantity limits
November 2018	Annual review
March 2019	Annual review
March 2020	Annual review and reference update. Added “For newly diagnosed older adults, other cystic fibrosis options for F508del mutation should be considered” to regulatory status. Also added requirement that patients 6 and older have to t/f Symdeko per SME
March 2021	Revised ppFEV1 requirements so that they only apply to patients age 6 and older. Added renewal requirement for patients less than 6 years old to have symptom improvement or stabilization
June 2021	Annual review

September 2022	Annual review. Per PI update, changed age requirement to 1 year and older. Also updated quantity chart for packets to 168 per 84 days due to package sizing
December 2022	Annual review. Per SME, removed hemoglobin and eGFR requirements from initiation criteria
September 2023	Annual review and reference update
December 2023	Annual review and reference update
September 2024	Annual review

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on September 6, 2024 and is effective on October 1, 2024.

Appendix 1 - List of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Potentiators

Generic Name	Brand Name
ivacaftor	Kalydeco
ivacaftor/lumacaftor	Orkambi
ivacaftor/tezacaftor	Symdeko
ivacaftor/tezacaftor/elexacaftor	Trikafta