lumacaftor/ivacaftor (Orkambi)™

Policy # 00456
Original Effective Date: 08/19/2015
Current Effective Date: 12/14/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider lumacaftor/ivacaftor (Orkambi™)‡ for the treatment of cystic fibrosis to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for lumacaftor/ivacaftor (Orkambi) will be considered when the following criteria are met:

- Patient has a documented diagnosis of cystic fibrosis; AND
- Patient is 2 years of age or older; AND
- Patient is homozygous for the Phe508del (F508del) mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) as detected by a U.S. Food and Drug Administration (FDA) cleared test. Homozygous refers to the presence of the F508del mutation on both alleles of the CFTR gene.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of lumacaftor/ivacaftor (Orkambi) when patient selection criteria are not met to be **investigational.***

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Background/Overview

Cystic fibrosis is a serious genetic disorder affecting the lungs and other organs that ultimately leads to an early death. It is caused by mutations (defects) in a gene that encodes for a protein called CFTR (cystic fibrosis transmembrane conductance regulator) that regulates ion (such as chloride) and water transport in the body. The defect in chloride and water transport 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.

Orkambi is a CFTR potentiator, indicated for the treatment of cystic fibrosis in patients age 2 years and older who are homozygous for the F508del mutation in the CFTR gene. The F508del mutation is the most common mutation in the CFTR gene (present in about 86% of individuals with cystic fibrosis). Among those with the F508del mutation, it is estimated that approximately 46.5% have two copies (homozygous) while 39.9% have one copy (heterozygous). The efficacy and safety of Orkambi have not been established in patients with cystic fibrosis other than those homozygous for the F508del mutation. Orkambi is supplied as tablets containing 200mg of lumacaftor and 125mg of ivacaftor as well as tablets and packets of granules containing 100 mg of lumacaftor and 125 mg of ivacaftor and packets of granules containing 150 mg lumacaftor and 188 mg ivacaftor. Orkambi is taken as two tablets (200 mg/125 mg) every 12 hours in patients that are 12 years of age and older. Pediatric patients that are 6 through 11 years of age take two tablets (100 mg/125 mg) every 12 hours. Pediatric patients that are 2 through 5 years of age take one lumacaftor 100 mg/ivacaftor 125 mg packet of granules every 12 hours if patient weight is less than 14 kg and one lumacaftor 150 mg/ivacaftor 188 mg packet of granules every 12 hours if weight is 14 kg or greater.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Orkambi is a CFTR potentiator, indicated for the treatment of cystic fibrosis in patients age 2 years and older who are homozygous for the F508del mutation in 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. The original indication was for patients 12 years of age and older, however in late 2016, the FDA approved Orkambi's use in those 6 years of age and older and in August 2018 the indication was expanded again to include patients 2 years of age and older.

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Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Orkambi in patients at least 12 years of age with cystic fibrosis who were homozygous for the F508del mutation in the CFTR gene was evaluated in two randomized, double-blind, placebo controlled, 24 week clinical trials in 1108 patients. Patients in both trials were randomized to receive either Orkambi 400/250mg every 12 hours, lumacaftor 600mg once daily, or placebo. The primary efficacy endpoint in both trials was the change in lung function as determined by absolute change from baseline in the percent of predicted forced expiratory volume in 1 second ($ppFEV_1$) at week 24. The $ppFEV_1$ was calculated by averaging the mean absolute change at week 16 and the mean absolute change at week 24. In TRAFFIC, the mean absolute change from baseline in $ppFEV_1$ at 24 weeks in patients treated with Orkambi was 2.6% ($p<0.001$ vs. placebo). In TRANSPORT, the mean absolute change from baseline in $ppFEV_1$ at 24 weeks in patients treated with Orkambi was 3.0% ($p<0.001$ vs. placebo).

The efficacy of Orkambi in children ages 6 through 11 years is extrapolated from efficacy in patients ages 12 years and older homozygous for the F508del mutation in the CFTR gene with support from population kinetic analyses showing similar drug exposure levels in patients ages 12 years and older and in children ages 6 through 11 years. Additional safety data was also obtained via studies. The safety profile of Orkambi in children 6 through 11 years of age was similar to those children that were 12 years of age and older. Spirometry was assessed as a safety endpoint. The within-group LS mean absolute change in $ppFEV_1$ from week 24 at week 26 was -3.2 percentage points.

Approval of Orkambi in children as young as age 2 was based on a phase 3 open-label study in 60 patients that showed that treatment with the drug for 24 weeks was generally safe and well tolerated, with a safety profile similar to that in patients aged 6 years and older.

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References

1. Orkambi. [package insert]. Vertex Pharmaceuticals. Boston, Massachusetts. Updated 08/2018.
2. Orkambi prior authorization document. Express Scripts. Updated 07/2015.

Policy History

Original Effective Date: 08/19/2015
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08/06/2015	Medical Policy Committee review
08/19/2015	Medical Policy Implementation Committee approval. New policy.
09/08/2016	Medical Policy Committee review
09/21/2016	Medical Policy Implementation Committee approval. New policy.
11/03/2016	Medical Policy Committee review
11/16/2016	Medical Policy Implementation Committee approval. Changed age from 12 years to 6 years based on the updated FDA approved indication
11/02/2017	Medical Policy Committee review
11/15/2017	Medical Policy Implementation Committee approval. No change to coverage.
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. Changed minimum age from 6 years to 2 years based on the updated FDA approved indication.
11/07/2019	Medical Policy Committee review
11/13/2019	Medical Policy Implementation Committee approval. No change to coverage.
11/05/2020	Medical Policy Committee review
11/11/2020	Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 11/2021

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

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NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.