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Medication Policy Manual	**Policy No:** dru409
Topic: Orkambi™, lumacaftor/ivacaftor	**Date of Origin:** July 10, 2015
Committee Approval Date: February 17, 2017	**Next Review Date:** February 2018
Effective Date: March 1, 2017	

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Lumacaftor/ivacaftor (Orkambi) is an orally administered medication used for the treatment of patients with cystic fibrosis (CF) who have two copies of the *F508del* mutation, the most common CF mutation.

Policy/Criteria

I. Most contracts require prior authorization approval of lumacaftor/ivacaftor (Orkambi) prior to coverage. Lumacaftor/ivacaftor (Orkambi) may be considered medically necessary in patients when criteria A, B, and C below are met:

A. A diagnosis of cystic fibrosis (CF)

AND

B. Confirmation that the patient has two copies of the *F508del* mutation (i.e. the patient is homozygous for the *F508del* mutation)

AND

C. The patient is at least six years of age

II. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers lumacaftor/ivacaftor (Orkambi) to be a self-administered medication.

B. When prior authorization is approved, lumacaftor/ivacaftor (Orkambi) may be authorized in quantities of 120 tablets per month.

C. Authorization shall be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Lumacaftor/ivacaftor (Orkambi) is considered investigational when used for all other conditions, including but not limited to:

A. Patients who are heterozygous for the *F508del* mutation (i.e. patients with only one copy of the *F508del* mutation)

B. Patients with any other mutation of the CFTR gene (e.g. *G551D*, *S1251N*, *R117H*)

Position Statement

Summary

- Cystic fibrosis (CF) is caused by a mutation in the CFTR gene that results in an inability to regulate water and minerals (specifically chloride) across epithelial linings, particularly in the lungs and gastrointestinal (GI) tract.
- There are many specific mutations that lead to CF; however, the most common CF mutation is the *F508del* mutation. Approximately 50% of the CF population has two copies of the *F508del* mutation.
- Lumacaftor/ivacaftor (Orkambi) has demonstrated efficacy [i.e. improvement in percent predicted of forced expiratory volume in one second ($ppFEV_1$) or in lung clearance index (LCI)] in patients six years of age or older who are homozygous (i.e. have two copies) for the F508del mutation. [1-4]
- The usual dose of lumacaftor/ivacaftor (Orkambi) are: lumacaftor 200 mg/ivacaftor 250 mg daily for patients age six to eleven years old, and lumacaftor 400 mg/ivacaftor 250 mg for patients age twelve or older.

Clinical Efficacy

The primary evidence of efficacy for lumacaftor/ivacaftor (Orkambi) in the treatment of CF comes from two replicate 24-week clinical studies (TRAFFIC and TRANSPORT). [1]

- The primary endpoint in the two phase 3 trials was the absolute change in $ppFEV_1$ from baseline at week 24.
- The patient population included in these trials consisted of stable CF patients twelve years or older who were homozygous for the *F508de*l mutation. These patients had ppFEV1 values between 40 and 90% of predicted normal values at the time of study entry.
- The treatment difference between lumacaftor/ivacaftor (Orkambi) and placebo as measured by the mean absolute change in $ppFEV_1$ from baseline was 3.3% in the pooled results of the TRAFFIC and TRANSPORT clinical trials.
- Significant secondary endpoints such as absolute change in body mass index (BMI) and quality of life demonstrated inconsistent results or failed to meet the minimal clinically important difference after hierarchical statistical testing.
- Lumacaftor/ivacaftor (Orkambi) has been approved for use in patients ages six to eleven years old based on the results of one double-blind, placebo-controlled trial and one open-label safety trial. [3-5]
- The recommended dose of lumacaftor/ivacaftor (Orkambi) for patients age twelve years and older is two tablets every twelve hours, each containing lumacaftor 200 mg/ivacaftor 125 mg (total daily dose of lumacaftor 800 mg/ivacaftor 500 mg). [2]
- The recommended dose for pediatric patients aged six to eleven years is two tablets, each containing lumacaftor 100 mg/ivacaftor 125 mg (total daily dose of lumacaftor 400 mg/ivacaftor 500 mg). [2]
- Efficacy and safety have not been demonstrated in any CF mutation outside of patients homozygous for the *F508del* mutation or in patients younger than six years of age. The safety and effectiveness of higher doses have not been established. [2]

Investigational Uses

- There are no published clinical trials evaluating the safety or efficacy of lumacaftor/ivacaftor (Orkambi) in patients younger than six years of age. Although lumacaftor/ivacaftor (Orkambi) is being studied for use in this population, there is currently no published evidence supporting its safety or efficacy in this setting. [6]
- In addition, there is no published evidence supporting the safety or efficacy of lumacaftor/ivacaftor (Orkambi) in patients with mutations other than F508del. Therefore, use in other mutations is considered investigational.

Cross References
Kalydeco®, ivacaftor, Medication Policy Manual, Policy No. 270

Codes	Number	Description
N/A		

References

1. Wainwright, CE, Elborn, JS, Ramsey, BW, et al. Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. *The New England journal of medicine*. 2015 Jul 16;373(3):220-31. PMID: 25981758
2. ORKAMBI™ [package insert]. Boston, MA: Vertex Pharmaceuticals Incorporated July 2015.
3. Study of Lumacaftor in Combination With Ivacaftor in Subjects 6 Through 11 Years of Age With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation. [cited 1/20/17]; Available from: https://clinicaltrials.gov/ct2/show/study/NCT01897233?term=lumacaftor+AND+ivacaftor&rank=2&sect=X0156
4. A Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects With CF, Homozygous for the F508del-CFTR Mutation. [cited 1/22/17]; Available from: https://clinicaltrials.gov/ct2/show/study/NCT02514473?term=lumacaftor+AND+ivacaftor&rank=12
5. U.S. Food and Drug Administration Approves ORKAMBI® (lumacaftor/ivacaftor) for Use in Children with Cystic Fibrosis Ages 6 through 11 who have Two Copies of the F508del Mutation [Press Release]. [cited 1/20/17]; Available from: http://investors.vrtx.com/releasedetail.cfm?ReleaseID=991350
6. Drug Development Pipeline - lumacaftor + ivacaftor. [cited 5/6/2015]; Available from: http://www.cff.org/research/DrugDevelopmentPipeline/

Revision History

Revision Date	Revision Summary
2/17/2017	Changed Criteria I.C to allow for use in patients age six or older.
2/12/2016	No criteria changes with this annual update.