VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Orkambi™ (lumacaftor/ivacaftor tablets and oral granules – Vertex)

TAC APPROVAL DATE: 07/10/2019

OVERVIEW

Orkambi, a combination of lumacaftor and ivacaftor, is indicated for the treatment of cystic fibrosis (CF) in patients ≥ 2 years 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 CF 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 CF other than those homozygous for the F508del mutation. Orkambi contains a new 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 granules]), a CFTR potentiator that enhances chloride transport of CFTR on the cell surface. The F508del mutation in CFTR causes CF by limiting the amount of CFTR protein that reaches the epithelial cell surface.

In patients with CF, mutations in both copies of the cystic fibrosis transmembrane conductance regulator (CFTR) gene disrupt normal production of the CFTR protein.[3] Different mutations cause CFTR to malfunction in different ways. In some people with CF, little to no CFTR is produced. In others, the defective protein is produced, but cannot move to the surface of the cell where it is needed to regulate the transfer of chloride and water in and out of cells. In others CFTR is produced and moves to the surface of the cell, but the gate that controls chloride movement does not open properly. The malfunctioning CFTR leads to an accumulation of unusually thick and stick mucus in the lungs, pancreas, and other organs. As new therapies are developed, it is very important for individuals to know which mutations are present. There are > 1,800 known CFTR mutations, many of which have been categorized into different groups. People with two mutations in classes I, II, and III typically exhibit more severe pulmonary disease and pancreatic insufficiency as compared to people with at least one mutation in classes IV and V. The F508del mutation is considered a class II mutation. Class II mutations are those in which the CFTR protein is created, but misfolded, keeping it from reaching the cell surface. According to the CF patient registry about 45.3% of patients have two copies of the F508del (Delta F508) mutation; about 40.9% of patients with CF have one F508del mutation; 13.7% of patients do not have an F508del mutation or it is unknown if they have such a mutation.[2]

The efficacy of Orkambi was established in two Phase III, randomized, double-blind, placebo-controlled, multicenter, pivotal studies in patients ≥ 12 years of age with CF who were homozygous for the F508del mutation in the CFTR gene.[3] In both studies, Orkambi was compared with placebo, as well as a different dose of the components contained within Orkambi (lumacaftor 600 mg once daily [QD] + ivacaftor 250 mg Q12H). The primary endpoint for both studies was the absolute change from baseline at Week 24 in the % of predicted forced expiratory volume in 1 second (FEV1), calculated by averaging the mean absolute change at Week 16 and the mean absolute change at Week 24. In TRAFFIC (n = 549), the mean absolute change (improvement) from baseline in FEV1 % predicted at 24 weeks in patients treated with Orkambi was 2.6% ($P < 0.001$ vs. placebo). In TRANSPORT (n = 599), the mean absolute change (improvement) from baseline in FEV1 % predicted at 24 weeks in patients treated with Orkambi was 3.0% ($P < 0.001$ vs. placebo).

The efficacy of Orkambi in children 6 through 11 years of age is extrapolated from efficacy in patients ≥ 12 years of age homozygous for the *F508del* mutation in the *CFTR* gene with support from population pharmacokinetic analyses showing similar drug exposure levels in patients ages 12 years and older and in children ages 6 through 11 years.[1] Additional safety data were obtained from a 24-week, open-label, Phase 3 clinical trial in 58 patients aged 6 through 11 years, mean age 9 years (unpublished). This study evaluated subjects with a screening FEV_1 ≥40 (mean ppFEV1 91.4 at baseline [range: 55 to 122.7]). The safety profile of Orkambi in children 6 through 11 years of age was similar to those in patients ≥ 12 years of age. Spirometry was assessed as a planned safety endpoint. The within-group LS mean absolute change from baseline in FEV_1 at Week 24 was 2.5 percentage points. At the Week 26 safety follow-up visit (following a planned discontinuation) $FEV_1$was also assessed. The within-group LS mean absolute change in FEV1 from Week 24 at Week 26 was -3.2 percentage points.

Guidelines

Guidelines from the CF Foundation (January 2018) provide guidance on the use of CFTR therapy in patients with CF.[4] The Guideline is not intended to establish a standard of care, rather it is intended to represent an effort to summarize evidence and provide sensible clinical recommendations based on the evidence. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the evidence and develop recommendations. The Committee did not choose to evaluate the clinical situations for which recommendations have already been published (e.g., Kalydeco for patients ≥ 12 years of age who carry at least one copy of the G551D mutation or CF patients 2 to 5 years of age with gating mutations other than G551D, or if the issue was of low priority and unlikely to change clinical practice (e.g., Orkambi in patients homozygous for F508del). Data for consideration were collected through April 2016. Recommendations are provided below.

The recommendations for Orkambi vs. no CFTR modulator therapy in patients homozygous for F508del are presented in Table 1 below. The recommendations for these patients place a high value on the potential improvement of patient-important outcomes, such as lung function. There is an abundance of data from clinical trials that demonstrates significant clinical improvement in patient-important outcomes for patients' ≥ 12 years of age with baseline $ppFEV_1 \leq 90\%$ treated with Orkambi. For this reason, the Committee made a strong recommendation for treatment with moderate certainty in the evidence. Patients with baseline $ppFEV_1 > 90\%$ failed to demonstrate equivalent improvements but the ability of the Committee to draw conclusions was hindered a by small numbers of patients in this lung function cohort. Nonetheless, the Committee concluded that the potential for preservation of lung function and other outcomes justified a conditional recommendation in favor of treatment. Another consideration in the decision to prescribe Orkambi is the reported increased incidence of cough and chest tightness among patients of all ages with $ppFEV_1 < 40\%$. Patients have generally tolerated gradual reintroduction of therapy but early worsening of symptoms should be included in treatment discussions.

Table 1. CFF Recommendations for Orkambi in Patients Homozygous for F508del Mutation.[4]

Age	$ppFEV_1$	Certainty	Recommendation
0 to 5 years	N/A	N/A	No Recommendation
6 to 11 years	< 40%	Very Low	Conditional For
	40% to 90%	Very Low	Conditional For
	> 90%	Very Low	Conditional For
12 to 17 years	< 40%	Moderate	Strong For
	40% to 90%	Moderate	Strong For
	> 90%	Low	Conditional For
18+ years	< 40%	Moderate	Strong For
	40% to 90%	Moderate	Strong For
	> 90%	Low	Conditional For

CFF – Cystic fibrosis foundation; $ppFEV_1$ – Percent predicted forced expiratory volume in 1 second; N/A – Not applicable.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Orkambi. 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, initial approval requires Orkambi to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 3 year in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

1. **Cystic Fibrosis (CF), Homozygous for the F508del (Phe508del) Mutation in the Cystic Fibrosis Transmembrane Regulator (CFTR) Gene.** Approve for 3 years in patients who meet the following criteria (A, B, and C):
   - **A)** The patient is homozygous for the F508del (Phe508del) mutation in the CFTR gene (meaning the patient has two copies of the F508del [Phe508del] mutation); AND
   - **B)** The patient is ≥ 2 years of age; AND
   - **C)** Orkambi is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of CF.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Orkambi has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Cystic Fibrosis, Heterozygous for the F508del (Phe508del) Mutation in the CFTR Gene.** Orkambi is not indicated for patients with only one copy of the F508del mutation in the CFTR gene.[1] Patients who are heterozygous for the F508del mutation and have one of the following mutations are

potential candidates for Kalydeco therapy: G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D, or R117H.

2. **Combination Therapy with Kalydeco or Symdeko.** Orkambi contains ivacaftor, the active agent in Kalydeco and therefore is not indicated in combination with Kalydeco. Symdeko contains ivacaftor and is therefore not indicated in combination with Orkambi.

3. 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® [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; August 2018.
2. CF patient registry 2017. Available at: https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2017-Patient-Registry-Annual-Data-Report.pdf. Accessed on June 26, 2019.
3. Wainwright CE, Elborn JS, Ramsey G, et al. Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for F508del CFTR. *N Engl J Med.* 2015; 373:220-231.
4. Ren CL, Morgan RL, Oermann C, et al. Cystic fibrosis foundation pulmonary guidelines: Use of CFTR modulator therapy in patients with cystic fibrosis. *Ann Am Thorac Soc*. 2018;15(3):271-280

OTHER REFERENCES UTILIZED

- Lahiri T, Hempstead SE, Brady C, et al. Clinical practice guidelines from the cystic fibrosis foundation for preschoolers with cystic fibrosis. *Pediatrics*. 2016;137(4).

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
New Policy	--	07/02/2015
Annual revision	No criteria changes.	07/20/2016
Selected revision	Added new age indication down to 6 years.	10/05/2016
Annual revision	No criteria changes.	07/12/2017
Annual revision	Added Symdeko to therapies Orkambi should not to be used in combination with.	07/11/2018
Selected revision	Added new age indication down to 2 years.	08/22/2018
Annual revision	No criteria changes	07/10/2019

TAC – Therapeutic Assessment Committee; DEU – Drug Evaluation Unit; * For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx.