CLINICAL UPDATE

Brand Name	Orkambi®
Generic Name	lumacaftor and ivacaftor
Drug Manufacturer	Vertex Pharmaceuticals Incorporated

Clinical Update

TYPE OF CLINICAL UPDATE

New Strength/Updated Indication

FDA APPROVAL DATE

September 2, 2022

LAUNCH DATE

September 12, 2022

REVIEW DESIGNATION

Priority; Orphan

TYPE OF REVIEW

Type 3 - New Dosage Form; New Drug Application (NDA): 211358

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Orkambi® is a combination of ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, and lumacaftor, 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.

MECHANISMS OF ACTION

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. In vitro studies have demonstrated that both lumacaftor and ivacaftor act directly on the CFTR protein in primary human bronchial epithelial cultures and other cell lines harboring the F508del-CFTR mutation to increase the quantity, stability, and function of F508del-CFTR at the cell surface, resulting in increased chloride ion transport. In vitro responses do not necessarily correspond to in vivo pharmacodynamic response or clinical benefit.

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DOSAGE FORM(S) AND STRENGTH(S)

- Oral granules: Unit-dose packets of lumacaftor 75 mg and ivacaftor 94 mg; lumacaftor 100 mg and ivacaftor 125 mg; lumacaftor 150 mg and ivacaftor 188 mg.
- Tablets: lumacaftor 100 mg and ivacaftor 125 mg; lumacaftor 200 mg and ivacaftor 125 mg

DOSE & ADMINISTRATION

- Reduce dosage in patients with moderate or severe hepatic impairment.
- When initiating Orkambi® in patients taking strong CYP3A inhibitors, reduce Orkambi® dosage for the first week of treatment.

Table 1 – Dose and Administration

Age	Weight	Dose	Administration
1 through 2 years	7 kg to <9 kg	1 packet of lumacaftor 75 mg/ivacaftor 94 mg granules	Mixed with one teaspoon (5 ml) of soft food or liquid and administered orally every 12 hours with fat containing food
	9 kg to <14 kg	1 packet of lumacaftor 100 mg/ivacaftor 125 mg granules	
	≥14 kg	1 packet of lumacaftor 150 mg/ivacaftor 188 mg granules	
2 through 5 years	<14 kg	1 packet of lumacaftor 100 mg/ivacaftor 125 mg granules	
	≥14 kg	1 packet of lumacaftor 150 mg/ivacaftor 188 mg granules	
6 through 11 years	-	2 tablets of lumacaftor 100 mg/ivacaftor 125 mg (lumacaftor 200 mg/ivacaftor 250 mg per dose)	Taken orally every 12 hours with fat containing food
12 years and older	-	2 tablets of lumacaftor 200 mg/ivacaftor 125 mg (lumacaftor 400 mg/ivacaftor 250 mg per dose)	

EFFICACY

Dose Ranging

Dose ranging for the clinical program consisted primarily of one double-blind, placebo-controlled, multiple-cohort trial which included 97 Caucasian patients with CF (homozygous for the F508del mutation) 18 years of age and older with a screening ppFEV1 ≥40. In the trial, 76 patients (homozygous for the F508del mutation) were randomized to receive lumacaftor alone at once daily doses of 200 mg, 400 mg, or 600 mg or 400 mg q12h for 28 days followed by the addition of ivacaftor 250 mg q12h and 27 patients (homozygous or heterozygous for the F508del mutation) received placebo. During the initial 28-day lumacaftor monotherapy period, treatment with lumacaftor demonstrated a dose-dependent decrease in ppFEV1 compared to placebo. Changes from Day 1 at Day

28 in ppFEV1 compared to placebo were 0.24, -1.4, -2.7, and -4.6 for the 200 mg once daily, 400 mg once daily, 600 mg once daily, and 400 mg q12h lumacaftor doses, respectively. Following the addition of ivacaftor 250 mg q12h, the changes from Day 1 at Day 56 in ppFEV1 compared to placebo were 3.8, 2.7, 5.6, and 4.2, respectively. Sweat chloride was also assessed in this trial. Following the initial 28 days of lumacaftor monotherapy, the changes from Day 1 at Day 28 in sweat chloride compared to placebo were -4.9, -8.3, -6.1, and -8.2 mmol/L for the 200 mg once daily, 400 mg once daily, 600 mg once daily, and 400 mg q12h lumacaftor doses, respectively. Following the addition of ivacaftor 250 mg q12h, the changes from Day 1 at Day 56 in sweat chloride compared to placebo were -5.0, -9.8, -9.5, and -11 mmol/L, respectively.

These data supported the evaluation of lumacaftor 400 mg/ivacaftor 250 mg q12h (Orkambi®) and lumacaftor 600 mg once daily/ivacaftor 250 mg q12h in the confirmatory trials.

Confirmatory

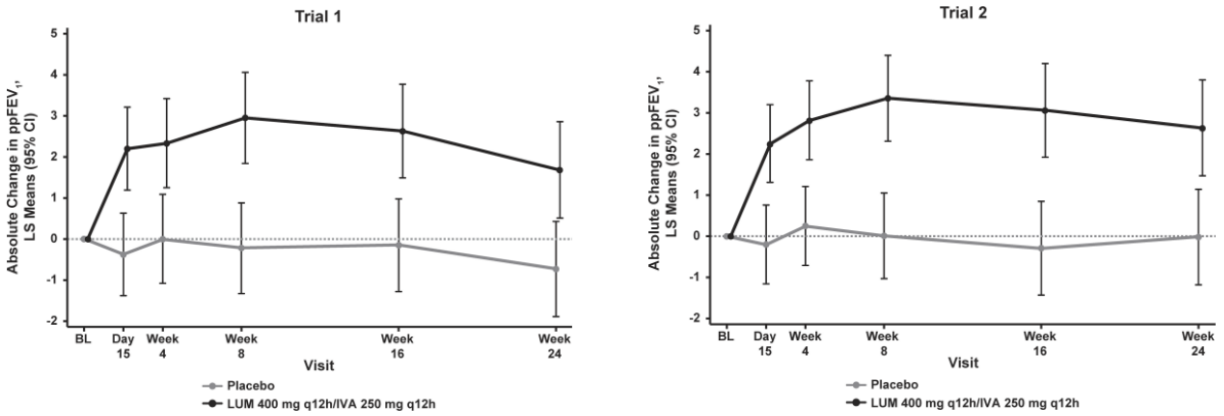
The efficacy of Orkambi® in patients with CF who are homozygous for the F508del mutation in the CFTR gene was evaluated in two randomized, double-blind, placebo-controlled, 24-week clinical trials (Trials 1 and 2) in 1108 clinically stable patients with CF of whom 369 patients received Orkambi® twice daily.

Trial 1 evaluated 549 patients with CF who were aged 12 years and older (mean age 25.1 years) with ppFEV1 at screening between 40-90 [mean ppFEV1 60.7 at baseline (range: 31.1 to 94.0)]. Trial 2 evaluated 559 patients aged 12 years and older (mean age 25.0 years) with ppFEV1 at screening between 40-90 [mean ppFEV1 60.5 at baseline (range: 31.3 to 99.8)]. Patients with a history of colonization with organisms such as Burkholderia cenocepacia, Burkholderia dolosa, or Mycobacterium abscessus, or who had 3 or more abnormal liver function tests (ALT, AST, AP, GGT ≥3 x the ULN or total bilirubin ≥2 x the ULN) were excluded.

Patients in both trials were randomized 1:1:1 to receive either Orkambi® (lumacaftor 400 mg q12h/ivacaftor 250 mg q12h; or lumacaftor 600 mg once daily/ivacaftor 250 mg q12h) or placebo. Patients took the study drug with fat-containing food for 24 weeks in addition to their prescribed CF therapies (e.g., bronchodilators, inhaled antibiotics, dornase alfa, and hypertonic saline).

The primary efficacy endpoint in both trials was change in lung function as determined by absolute change from baseline in ppFEV1 at Week 24, assessed as the average of the treatment effects at Week 16 and at Week 24. In both trials, treatment with Orkambi® resulted in a statistically significant improvement in ppFEV1. The treatment difference between Orkambi® and placebo for the mean absolute change in ppFEV1 from baseline at Week 24 (assessed as the average of the treatment effects at Week 16 and at Week 24) was 2.6 percentage points [95% CI (1.2, 4.0)] in Trial 1 (P=0.0003) and 3.0 percentage points [95% CI (1.6, 4.4)] in Trial 2 (P<0.001). These changes persisted throughout the 24-week treatment period (Figure 1). Improvements in ppFEV1 were observed regardless of age, disease severity, sex, and geographic region.

Figure 1. Absolute Change From Baseline at Each Visit in Percent Predicted FEV_1 in Trial 1 and Trial 2.



LS = least squares; q12h = every 12 hours

Key secondary efficacy variables included relative change from baseline in ppFEV1 at Week 24, assessed as the average of the treatment effects at Week 16 and at Week 24; absolute change from baseline in BMI at Week 24; absolute change from baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain score at Week 24, a measure of respiratory symptoms relevant to patients with CF such as cough, sputum production, and difficulty breathing; proportion of patients achieving ≥5% relative change from baseline in ppFEV1 using the average of Week 16 and Week 24; and number of pulmonary exacerbations through Week 24. For the purposes of these trials, a pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) as a result of 4 or more of 12 pre-specified sino-pulmonary signs/symptoms.

Table 2: Summary of Other Efficacy Endpoints in Trials 1 and 2*

		Trial 1		Trial 2	
		Placebo (n=184)	Orkambi® **LUM 400 mg q12h/IVA 250 mg q12h (n=182)**	**Placebo (n=187)**	Orkambi® **LUM 400 mg q12h/IVA 250 mg q12h (n=187)**
Relative change in $ppFEV_1$ at Week 24† (%)	Treatment difference (95% CI)	–	4.3 (1.9, 6.8) *P*=0.0006‡	–	5.3 (2.7, 7.8) *P*<0.0001‡
Absolute change in BMI at Week 24 (kg/m^2)	Treatment difference (95% CI)	–	0.1 (-0.1, 0.3)	–	0.4 (0.2, 0.5) *P*=0.0001‡
Absolute change in CFQ-R Respiratory Domain Score (Points) at Week 24	Treatment difference (95% CI)	–	1.5 (-1.7, 4.7)	–	2.9 (-0.3, 6.0)
Proportion of patients with ≥5% relative change in $ppFEV_1$ at Week 24†	%	22%	37%	23%	41%
	Odds ratio (95% CI)	–	2.1 (1.3, 3.3)	–	2.4 (1.5, 3.7)
Number of pulmonary exacerbations through Week 24	# of events (rate per 48 weeks)	112 (1.1)	73 (0.7)	139 (1.2)	79 (0.7)
	Rate ratio (95% CI)	–	0.7 (0.5, 0.9)	–	0.6 (0.4, 0.8)

* In each trial, a hierarchical testing procedure was performed within each active treatment arm for primary and secondary endpoints vs. placebo; at each step, $P \leq 0.0250$ and all previous tests also meeting this level of significance was required for statistical significance.

† Assessed as the average of the treatment effects at Week 16 and Week 24.

‡ Indicates statistical significance confirmed in the hierarchical testing procedure. Other efficacy measures considered not statistically significant.