New Drug Overview
Orkambi® (lumacaftor/ivacaftor)

- **Overview/Summary:** Cystic fibrosis (CF) is a rare, life-threatening autosomal recessive disease. The frequency is approximately 1:2,000 to 3,000 live births. CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene which codes for the CFTR protein.[1] The CFTR protein functions as a channel across the membrane of cells that produce mucus, sweat, saliva, tears and digestive enzymes. The channel transports chloride ions into and out of cells. This transport helps control the movement of water in tissues, necessary for the production of thin, freely flowing mucus which provides a protective coating in the airways, digestive system, reproductive system and other organs and tissues. In addition to chloride, the CFTR gene also transports sodium ions across cell membranes for lung and pancreatic function.[2]

  Typical respiratory manifestations of CF include a persistent and productive cough, hyperinflation of the lung fields on chest radiograph, pulmonary function tests consistent with obstructive airway disease, as well as colonization of the airway with pathogenic bacteria early in life. In terms of the gastrointestinal manifestations, patients experience progressive pancreatic disease in the form of pancreatic insufficiency, pancreatitis and CF-related diabetes. Furthermore, malnutrition due to pancreatic insufficiency may cause rectal prolapse and musculoskeletal disorders. Patients with CF are also at an increased risk of liver disease, infertility, venous thrombosis and nephrolithiasis.[1]

  Orkambi® (lumacaftor/ivacaftor) is a combination product that contains ivacaftor, a potentiator of the CFTR protein as well as lumacaftor, a CFTR corrector. This co-formulated product is the first medication that has been Food and Drug Administration (FDA)-approved to target the underlying cause of CF in patients that are homozygous for the F508del mutation, which is the most prevalent mutation among patients in the United States.[3] It is estimated that of the 30,000 individuals in the United States that have CF, approximately 8,500 have two copies of the F508del mutation.[4]

  The Cystic Fibrosis Foundation (CFF) currently has numerous guidelines available to help with the diagnosis and management of the various complications associated with CF. The most recent guidelines from 2013 that address chronic medications for the maintenance of lung health include dornase alfa, inhaled hypertonic saline, antibiotics such as inhaled tobramycin, inhaled aztreonam or oral azithromycin if *Pseudomonas aeruginosa* is persistently present, and Kalydeco® (ivacaftor).[5] These guidelines have not yet been updated to include this newest agent, Orkambi® (lumacaftor/ivacaftor).

Table 1. Dosing and Administration[1]

Generic Name	Adult Dose	Pediatric Dose	Availability
Lumacaftor/ ivacaftor	Cystic Fibrosis (homozygous for F508del): Tablet: initial, maintenance and maximum, 400 mg/250 mg every 12 hours with fat-containing foods Dosage Adjustment for Patients with Moderate Hepatic Impairment (Child-Pugh Class B): 400 mg/500 mg QAM and 200 mg/125 mg QPM with fat-containing foods Dosage Adjustment for Patients with Severe Hepatic Impairment	Cystic Fibrosis (homozygous for F508del) 6 to ≤11 years of age: Tablet: initial, maintenance and maximum, 200 mg/250 mg every 12 hours with fat-containing foods Cystic Fibrosis (homozygous for F508del) ≥12 years of age: See adult dosing.	Tablet: 100 mg/125 mg 200 mg/125 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	(Child-Pugh Class C): Use with caution: maximum dose of: 200 mg/125 mg every 12 hours with fat-containing foods Dosage Adjustment for Patients Taking CYP3A Inhibitors: No dosage adjustment required when CYP3A inhibitors are initiated in patients already taking lumacaftor/ivacaftor. However, when initiating lumacaftor/ivacaftor in patients currently taking strong CYP3A inhibitors, reduce dose: One tablet QD for one week then increase to the recommended daily dose of two tablets every 12 hours.		

Evidence-based Medicine

- Several phase II studies were performed with the investigational agent, lumacaftor, both alone and in combination with ivacaftor to evaluate the safety and tolerability of these products in CF individuals over the age of 18 years with the F508del-CFTR mutation.
    - Four doses of lumacaftor were found to have a similar adverse event profile to placebo during a 28 day trial. In addition, this agent was found to reduce sweat chloride values in a dose-dependent manner with only the 100 mg and 200 mg groups achieving statistical significance ($P<0.05$ and $P<0.01$, respectively). There were no significant changes in lung function in any of the dose groups.[6]
    - The second phase II trial, was also a randomized, double-blind, placebo-controlled trial that examined three successive cohorts. The results from each cohort were used to assist with the appropriate dose selection for the subsequent cohort.[7]
        - Cohort 1 (homozygous for the F508del mutation) was randomized to either placebo for 21 days or lumacaftor 200 mg once daily for 14 days followed by the addition of either ivacaftor 150 mg or 250 mg every 12 hours for seven days. For the combination period, mean sweat chloride fell significantly only for those individuals assigned to the lumacaftor 200 mg plus ivacaftor 250 mg group compared with placebo ($P<0.001$). In addition, the change in sweat chloride concentration over the 21-day study period for patients given lumacaftor 200 mg plus ivacaftor 250 mg was -12.6 mmol/L ($P<0.001$) compared to day one and -10.9 mmol/L ($P=0.002$) compared with placebo.
        - Cohorts 2 and 3 (F508del CFTR homozygous and heterozygous individuals) were randomly assigned to either 56 days of placebo or lumacaftor with ivacaftor 250 mg every 12 hours added after 28 days. Results from Cohort 2 and 3 showed that there was no significant decrease in mean sweat chloride concentration during the combination treatment in any treatment group. In Cohort 2, the lumacaftor 600 mg combination group significantly improved FEV1 by 5.6 percentage points ($P=0.013$) compared to placebo from day 1 to 56. In Cohort 3, FEV1 improvement of 7.7 percentage points ($P=0.003$) was observed during the combination treatment period.
    - Phase III studies (TRAFFIC and TRANSPORT) showed that statistically significant mean absolute improvements in FEV_1 compared to placebo, with a range of 2.6 to 4.0 percentage points ($P\leq0.0004$) and a mean relative improvement of 4.3 to 6.7% ($P\leq0.0007$). In addition, the pooled analysis from these phase III trials showed statistically significant reductions of 30 to 39% in the rate of pulmonary exacerbations for those who received the combination

regimens compared to those who received placebo (P≤0.0014) as well as statistically significant improvement in the body mass index (P<0.0001).[8,9]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - The most recent guidelines from 2013 that address chronic medications for the maintenance of lung health include dornase alfa, inhaled hypertonic saline, antibiotics such as inhaled tobramycin, inhaled aztreonam or oral azithromycin if Pseudomonas aeruginosa is persistently present, and Kalydeco® (ivacaftor).[5] These guidelines have not yet been updated to include this newest agent, Orkambi® (lumacaftor/ivacaftor).

- Other Key Facts:
  - This is the first medication that specifically targets CF individuals with two copies of the F508del mutation.
  - Safety and effectiveness of this agent in individuals < 12 years of age is unknown at this time.
  - Long term efficacy data is unavailable at this time.

References

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