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; maximum: Two tablets every 12 hours with fat-containing foods Dosage Adjustment for Patients with Moderate Hepatic Impairment (Child-Pugh Class B): Two tablets QAM and one tablet QPM with fat-containing foods Dosage Adjustment for Patients with Severe Hepatic Impairment (Child-Pugh Class C):	See adult dose. Safety and efficacy in children less than 12 years of age have not been established.	Tablet: 200 mg/125 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Use with caution: maximum dose of: One tablet 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 a 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 ($P\leq0.0014$) 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.

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New Drug Review
Orkambi® (lumacaftor/ivacaftor)

Overview/Summary

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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).

Indications

Lumacaftor/ivacaftor is indicated for the treatment of CF in patients age 12 years 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.

Pharmacokinetics

Table 1. Pharmacokinetics[3]

Generic Name	Tmax (hours)	Bound to plasma proteins (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
lumacaftor/ ivacaftor	4*	99	~8.6 (lumacaftor)- 51% excreted	Lumacaftor not extensively metabolized;	25.2 (lumacaftor) 9.34 (ivacaftor)

Generic Name	Tmax (hours)	Bound to plasma proteins (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
			in feces 6.6 (ivacaftor)-87.8% excreted in feces	Ivacaftor primarily metabolized by CYP3A, M1 and M6 major metabolites	

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Clinical Trials

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. The first randomized, double-blind, placebo-controlled study evaluated the use of four different strengths of lumacaftor compared to placebo for individuals that are homozygous for the F508del mutation. Lumacaftor was found to have a similar adverse event profile to placebo during the 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 (forced expiratory volume in one second [FEV_1], forced vital capacity [FVC], forced expiratory flow at 25 to 75% [$FEF_{25-75\%}$]) 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. In Cohort 1, the chosen individuals were homozygous for the F508del mutation and were randomized to either placebo for 21 days or lumacaftor 200 mg once daily for 14 days followed by the addition of either ivacaftor 150mg 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 (-9.1 mmol/L, 95% confidence interval [CI], 12.9 to -5.4; 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 (-17.2 to -7.9; P<0.001) compared to day one and -10.9 mmol/L (-17.6 to -4.2; P=0.002) compared with placebo.[7]

Cohorts 2 and 3 included F508del CFTR homozygous and heterozygous individuals, randomly assigned to either 56 days of placebo or lumacaftor (Cohort 2: 200 mg, 400 mg or 600 mg once daily; Cohort 3: 400mg every 12 hours) 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 FEV_1 by 5.6 percentage points (P=0.013) compared to placebo from day 1 to 56. In Cohort 3, FEV_1 improvement of 7.7 percentage points (P=0.003) was observed during the combination treatment period. Patients who were heterozygous for the F508del CFTR mutation did not experience a significant improvement in $FEV_{1.}$ The total proportion of adverse events and serious adverse events was similar between those receiving combination treatment and placebo. In addition, the incidence of chest tightness and dyspnea increased during the monotherapy period with higher doses of lumacaftor.[7]

The most recent results from two large phase III trials (TRAFFIC and TRANSPORT) with the combination of ivacaftor and lumacaftor for the treatment of patients with two copies of the F508del mutation were recently released. Results showed that all four 24-week treatment arms achieved statistically significant mean absolute improvements in FEV_1 compared to placebo, with a range of 2.6 to 4.0 percentage points (P≤0.0004) and a mean relative improvement of 4.3 to 6.7% (P≤0.0007). 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). The combination product was generally well tolerated with the most common adverse events, regardless of treatment group, being infective pulmonary exacerbation, cough, headache and increased sputum.[8,9]

Table 2. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Clancy et al[6†] Group A: VX-809 25 mg or 50 mg QD vs placebo Group B VX-809 100 mg or 200 mg QD vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with a documented diagnosis of CF, sweat chloride value ≥60 mmol/L, F508del-CFTR mutation on both alleles and a FEV_1 of at least 40% of predicted normal for age, gender and height	N=89 28 days for both groups	Primary: Safety and tolerability of VX-809 Secondary: Evaluation of pharmacodynamic impact on CFTR function (sweat chloride and NPD), spirometry to measure pulmonary function, CFQ-R	Primary: The type and incidence of adverse events were similar among VX-809 groups and placebo-treated groups. Respiratory events were the most commonly reported type of adverse event, with cough occurring in 46% of VX-809-treated individuals and 41 % of placebo-treated individuals. There was no difference in the incidence of physician-diagnosed pulmonary exacerbations between the VX-809 and the placebo-treated individuals (17% vs 12%; P=0.62). Four individuals, one from each of the VX-809 dose groups, discontinued study drug compared with none from the placebo-treated group. All were due to the occurrence of respiratory adverse events. Secondary: There were no individuals classified as responders in the 25 or 50 mg dose groups for reduction in the sweat chloride values. The mean treatment differences from baseline for the 100 mg and 200 mg groups were found to be statistically significant compared to placebo (-6.13 mmol/L; 95% CI, 12.25 to -0.01; P<0.05 and -8.21 mmol/L (95% CI, 14.33 to -2.10; P<0.01), respectively. There were no significant changes in CFTR-dependent NPD parameters in any of the dose groups. There were no significant changes in lung function (FEV_1, FVC, $FEF_{25-75\%}$) in any of the dose groups. There were no clear or sustained changes in the respiratory domain or in any other subdomains of the CFQ-R in any dose group.
Boyle et al[7†] **Cohort 1:** Lumacaftor 200 mg QD for 14 days followed by lumacaftor 200 mg QD plus ivacaftor 150 mg Q12H for 7 days vs	DB, MC, PC, RCT **Cohort 1:** Patients ≥ 18 years of age with a documented diagnosis of CF, phe508del CFTR homozygous and forced expiratory volume in one second	**Cohort 1:** N=64 21 days **Cohort 2:** *Homozygous phe508del:* N=82	**Cohort 1** Primary: Change in CFTR function as measured by change in sweat chloride concentration during combination treatment (from day 14 to day 21) as well as safety assessments	**Cohort 1** Primary: The sweat chloride concentration decreased during the lumacaftor monotherapy period for both treatment groups but neither was significant (P=0.015 for the ivacaftor 150 mg group and P=0.046 for the ivacaftor 250 mg group). For the combination period, mean sweat chloride decreased by 9.1 mmol/L for those individuals assigned to the lumacaftor 200 mg plus ivacaftor 250 mg group compared to placebo (95% CI, 12.9 to -5.4;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
lumacaftor 200 mg QD for 14 days followed by lumacaftor 200 mg QD plus ivacaftor 250 mg Q12H for 7 days vs placebo for 21 days **Cohort 2** *Homozygous phe508del:* Lumacaftor 200 mg QD for 28 days followed by lumacaftor 200 mg QD plus ivacaftor 250 mg Q12H for 28 days vs Lumacaftor 400 mg QD for 28 days followed by lumacaftor 400 mg QD plus ivacaftor 250 mg Q12H for 28 days vs Lumacaftor 600 mg QD for 28 days followed by lumacaftor 600 mg QD plus ivacaftor 250 mg Q12H for 28 days	(FEV_1) of at least 40% of predicted **Cohort 2:** Patients ≥ 18 years of age with a documented diagnosis of CF, phe508del CFTR homozygous and forced expiratory volume in one second (FEV_1) of at least 40% of predicted (Also included a subgroup of individuals heterozygous for phe508del CFTR and those who had a second CFTR mutation either predicted to eliminate CFTR protein production or known to not respond to ivacaftor on the basis of in-vitro testing) **Cohort 3:** Patients ≥ 18 years of age with a documented diagnosis of CF, phe508del CFTR homozygous and forced expiratory volume in one second (FEV_1) of at least 40% of predicted	*Heterozygous phe508del:* N=27 56 days **Cohort 3:** N=15 56 days	Secondary: Absolute change in predicted FEV_1 at days 7, 14, and 21 and change in sweat chloride from baseline to day 14 **Cohort 2** Primary: Change of CFTR function as measured by change in sweat chloride concentration during combination treatment and safety Secondary: Absolute change in predicted FEV_1 at days 14, 28, 42, and 56, change in sweat chloride concentration from baseline at days 28 and 56, change in CFQ-R score at days 14, 28, 42, and 56 **Cohort 3** Primary: Change in CFTR function as measured by change in sweat chloride concentration during combination therapy and safety	P<0.001) but not for the lumacaftor 200 mg plus ivacaftor 150 mg group (P value not reported). 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 (-17.2 to -7.9; P<0.001) compared to day one and -10.9 mmol/L (-17.6 to -4.2; P=0.002) compared to placebo. No serious adverse events were reported but one individual discontinued lumacaftor monotherapy within seven days because of reported chest tightness. The most common adverse event during monotherapy and combination therapy was cough. Secondary: FEV_1 did not change significantly during monotherapy in any group. For the group receiving lumacaftor 200 mg plus ivacaftor 150 mg, the mean percent predicted FEV_1 increased significantly from day 14 to day 21 (3.5, 95% CI, 0.9 to 6.1; P=0.010). The change in FEV_1 for day 1 to 21 did not differ significantly between treatment and placebo groups (P=0.176). No significant changes were seen in the lumacaftor 200 mg plus ivacaftor 250 mg group. **Cohort 2 and Cohort 3** Primary: There was no significant decrease in mean sweat chloride concentration during combination treatment in any treatment group The total proportion of adverse events and serious adverse events was similar between those receiving combination treatment and placebo (no P values reported). The incidence of chest tightness and dyspnea increased during the monotherapy period with higher doses of lumacaftor. The most common adverse events during the monotherapy period included cough, pulmonary exacerbation, headache, productive cough, upper respiratory tract infection and chest tightness. The most common adverse events during the combination period included cough, pulmonary exacerbation and headache. Seven participants discontinued lumacaftor monotherapy due to adverse events but no participants

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo for 56 days *Heterozygous phe508del:* Lumacaftor 600 mg QD for 28 days followed by lumacaftor 600 mg QD plus ivacaftor 250 mg Q12H for 28 days vs. placebo for 56 days **Cohort 3:** Lumacaftor 400 mg Q12H for 28 days followed by lumacaftor 400 mg Q12H plus ivacaftor 250 mg Q12H for 28 days vs placebo for 56 days			Secondary: Absolute change in predicted FEV_1 at days 14, 28, 42, and 56, change in sweat chloride concentration from baseline at days 28 and 56, change in CFQ-R score at days 14, 28, 42, and 56	discontinued due to adverse events during the combination treatment period. Secondary: In Cohort 2, the lumacaftor 600mg group significantly improved the FEV_1 by 5.6 percentage points (P=0.013) primarily during the combination period compared to the placebo group from day 1 to 56. In Cohort 3, FEV_1 did not change significantly across the entire study period compared to placebo (4.2 percentage points; P=0.132). However, FEV_1 improvement was observed during the combination period compared with placebo (7.7 percentage points; P=0.003). Phe508del CFTR heterozygous patients did not have a significant improvement in FEV_1.
Wainwright et al[8] (TRAFFIC) Lumacaftor 600 mg QD plus ivacaftor 250 mg Q12H vs	DB, MC, PC, RCT Patients ≥ 12 years of age with documented CF and two copies of F508del mutation	N=549 24 weeks	Primary: Mean absolute change from baseline in $ppFEV_1$ at the end of the 24-week treatment period (as assessed by the average change in	Primary: Statistically significant mean absolute and relative improvements in lung function were observed for both treatment groups at all points during the study. For the lumacaftor 600 mg group the mean absolute change was 3.6 (P<0.0001) as compared with placebo (-0.44; P=0.4002). The lumacaftor 400 mg group had a mean absolute change of 2.2 (P<0.0001) as compared with placebo (-0.44; P=0.4002).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
lumacaftor 400 mg Q12H plus ivacaftor 250 mg Q12H vs placebo			lung function at week 16 and at week 24 analyzed using a MMRM) Secondary: Number of pulmonary exacerbations, change in body mass index, change in CFQ-R, proportion of patients with 5% or greater relative improvement in ppFEV$_1$	In regards to the mean relative change, the lumacaftor 600 mg group was 6.4% (P<0.0001) as compared with placebo (-0.34%; P=0.7113) and the lumacaftor 400 mg group was 4.0% (P<0.0001) as compared with placebo (-0.34%; P=0.7113). Secondary: Individuals who received the combination regimens experienced a 28 to 43% decrease in the rate of pulmonary exacerbations over the 24-week period compared to placebo. For the lumacaftor 600 mg group, the rate ratio of pulmonary exacerbations was 0.72 (P=0.0491). In the 400 mg group, the rate ratio of pulmonary exacerbations was 0.66 (P=0.0169). The difference between lumacaftor/ivacaftor and placebo for absolute change in BMI was not found to be significant for either treatment group: 0.16 (P=0.11) for the lumacaftor 600 mg group and 0.13 (P=0.19) for the lumacaftor 400 mg group. Change in the CFQ-R within groups showed 1.1 (P=0.3423) for placebo compared to 5.0 (P<0.0001) for the lumacaftor 600 mg group and 2.6 (P=0.0295) for the lumacaftor 400 mg group. Both treatment groups observed a statistically significant percentage of patients with at least a 5% greater relative improvement in ppFEV$_1$. For the lumacaftor 600 mg group, the odds ratio was 2.94 (P<0.0001) and for the lumacaftor 400 mg group, the odds ratio was 2.06 (P=0.0023).
Wainwright et al[8] (TRANSPORT) Lumacaftor 600 mg QD plus ivacaftor 250 mg Q12H vs lumacaftor 400 mg	DB, MC, PC, RCT Patients ≥ 12 years of age with documented CF and two copies of F508del mutation	N=559 24 weeks	Primary: Mean absolute change from baseline in pp FEV$_1$ at the end of the 24-week treatment period (as assessed by the average change in lung function at week 16 and at week 24	Primary: Statistically significant mean absolute and relative improvements in lung function were observed for both treatment groups at all points during the study. For the lumacaftor 600 mg group the mean absolute change was 2.5 (P<0.0001) as compared with placebo (-0.15; P=0.7744). The lumacaftor 400 mg group had a mean absolute change of 2.9 (P<0.0001) as compared with placebo (-0.15; P=0.7744). In regards to the mean relative change, the lumacaftor 600 mg group was 4.4% (P<0.0001) as compared with placebo 0.0%; P=0.9983) and the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Q12H plus ivacaftor 250 mg Q12H vs placebo			analyzed using a MMRM). Secondary: Number of pulmonary exacerbations, change in body mass index, change in CFQ-R, proportion of patients with 5% or greater relative improvement in ppFEV$_1$	lumacaftor 400 mg group was 5.3% (P<0.0001) as compared with placebo (0.0%; P=0.9983). Secondary: Individuals who received the combination regimens experienced a 28 to 43% decrease in the rate of pulmonary exacerbations over the 24-week period compared to placebo. For the lumacaftor 600 mg group, the rate ratio of pulmonary exacerbations was 0.69 (P=0.0116). In the 400 mg group, the rate ratio of pulmonary exacerbations was 0.57 (P=0.0002). The difference between lumacaftor/ivacaftor and placebo for absolute change in BMI was found to be significant for both treatment groups: 0.41 (P<0.001) for the lumacaftor 600 mg group and 0.36 (P<0.001) for the lumacaftor 400 mg group. Change in the CFQ-R within groups showed 2.8 (P=0.0152) for placebo compared to 5.0 (P<0.0001) for the lumacaftor 600 mg group and 5.7 (P<0.0001) for the lumacaftor 400 mg group. Both treatment groups observed a statistically significant percentage of patients with at least a 5% greater relative improvement in ppFEV$_1$. For the lumacaftor 600 mg group, the odds ratio was 2.96 (P<0.0001) and for the lumacaftor 400 mg group, the odds ratio was 2.38 (P=0.0001). Safety data was reported using pooled data from the TRAFFIC and TRANSPORT studies. The most common adverse events, regardless of group, were infective pulmonary exacerbation, cough, headache and increased sputum. More individuals in the combination treatment group discontinued treatment because of adverse events than in the placebo group (4.2% compared to 1.6%, P values not reported).

†Phase II study
Drug regimen abbreviations: QD=once daily
Study abbreviations: CI=confidence interval, DB=double-blind, MC=multicenter, PC=placebo-controlled, RCT=randomized controlled trial
BMI=body mass index, CF=cystic fibrosis, CFQ-R= Cystic Fibrosis Questionnaire-Revised, CFTR=cystic fibrosis transmembrane conductance regulator, FEV$_1$= forced expiratory volume in one second, FEF$_{25-75\%}$= forced expiratory flow at 25 to 75%, FVC=forced vital capacity, MMRM= Mixed Model for Repeated Measures, NPD= nasal potential difference, Phe508del=F508del, ppFEV$_1$= percent predicted forced expiratory volume in one second

Special Populations

Table 3. Special Populations[3]

Population	Precaution
Elderly	Safety and efficacy in elderly patients have not been established.*
Renal Dysfunction	Not studied in renal dysfunction.*
Hepatic Dysfunction	Following multiple doses of lumacaftor/ivacaftor for 10 days, subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) had approximately 50% higher exposures and approximately 30% higher Cmax for both lumacaftor and ivacaftor compared with healthy subjects matched for demographics. Not studied in severe hepatic dysfunction.*
Pregnancy / Nursing	Category: B Excretion through breast milk: probable; effects unknown therefore use with caution.
Children	FDA approved for use in children ages: 12 years of age and older. Safety and efficacy in children under 12 years of age have not been established.*
Medicare Part B Coverage	Not applicable

*No adequate or well-controlled trials.

Adverse Drug Events

The most common adverse drug events to lumacaftor/ivacaftor were dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infections, fatigue, abnormal respiration, increased blood creatinine phosphokinase, rash, flatulence, rhinorrhea and influenza.[3]

Table 4. Incidence of Adverse Events in ≥ 5% of patients with CF patients treated with Orkambi® who are Homozygous for the F508del Mutation in the CFTR Gene in Two Placebo-Controlled Phase III Trials of 24 Weeks Duration[3]

Adverse Event	Reported Frequency	
	Lumacaftor/ivacaftor 2 tablets every 12 hours n (%), N=369	Placebo n (%), N=370
Blood creatinine phosphokinase increased	27 (7)	20 (5)
Diarrhea	45 (12)	31 (8)
Dyspnea	48 (13)	29 (8)
Fatigue	34 (9)	29 (8)
Flatulence	24 (7)	11 (3)
Influenza	19 (5)	8 (2)
Nasopharyngitis	48 (13)	40 (11)
Nausea	46 (13)	28 (8)
Rash	25 (7)	7 (2)
Respiratory abnormal	32 (9)	22 (6)
Rhinorrhea	21 (6)	15 (4)
Upper respiratory tract infection	37 (10)	20 (5)

Contraindications

There are no contraindications for lumacaftor/ivacaftor.[3]

Warnings/Precautions

Table 5. Warnings and Precautions[3]

Warning/Precaution	Lumacaftor/ivacaftor
Patients with advanced liver disease; there have been reports of worsening of liver function in patients with advanced liver disease who are receiving lumacaftor/ivacaftor. Patients should be closely monitored after initiating therapy and dose should be reduced.	a
Liver-related events; elevated transaminases have been reported in some individuals receiving lumacaftor/ivacaftor. It is recommended to check ALT, AST and bilirubin before starting therapy and then every three months during the first year of treatment and then annually. Administration of lumacaftor/ivacaftor should be stopped if ALT or AST is greater than five times the upper limit of normal (ULN) when not associated with elevated bilirubin. If ALT or AST elevations are greater than three times ULN when associated with bilirubin elevations greater than two times ULN, lumacaftor/ivacaftor should be stopped.	a
Respiratory events; respiratory events (e.g., chest discomfort, dyspnea, and respiration abnormal) were observed more commonly in patients during initiation of lumacaftor/ivacaftor compared to those who received placebo. Clinical experience in patients with percent predicted FEV1 less than 40 is limited. It is recommended that additional monitoring of these patients should occur during initiation of therapy.	a
Cataracts; cases of non-congenital lens opacities have been reported in pediatric patients treated with ivacaftor. It is recommended that baseline and follow-up ophthalmological examinations be performed in pediatric patients initiating lumacaftor/ivacaftor treatment.	a

Drug Interactions

Table 6. Drug Interactions[3,5]

Generic Name	Interacting Medication or Disease	Potential Result
Lumacaftor/ ivacaftor	Digoxin and other P-gp substrates	Lumacaftor has the potential to both inhibit and induce P-gp and ivacaftor is a weak inhibitor of P-gp. Concomitant use may alter the exposure of these substrates and should be monitored.
Lumacaftor/ ivacaftor	Substrates of CYP3A	Administration of lumacaftor/ivacaftor may decrease exposure of medications that are substrates of CYP3A (including contraceptives) and thereby decrease their therapeutic effect. It is not recommended to co-administer lumacaftor/ivacaftor with CYP3A substrates that have a narrow therapeutic index such as midazolam, triazolam, cyclosporine, everolimus, sirolimus and tacrolimus.
Lumacaftor/ ivacaftor	Strong CYP3A inducers	Co-administration of lumacaftor/ivacaftor with strong CYP3A inducers (e.g., rifampin, St. John's Wort, phenytoin, etc.) is not recommended.
Lumacaftor/ ivacaftor	Strong CYP3A inhibitors	Co-administration of lumacaftor/ivacaftor with strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin,

Generic Name	Interacting Medication or Disease	Potential Result
		etc.) may increase the concentration of ivacaftor. If initiating lumacaftor/ivacaftor in patients taking a strong CYP3A inhibitor, it is recommended that the dose of lumacaftor/ivacaftor be reduced for the first week to one tablet daily and then the recommended daily dose can be initiated. No dosage adjustment is necessary when CYP3A inhibitors are started in patients already taking lumacaftor/ivacaftor.
Lumacaftor/ ivacaftor	CYP2B6 and CYP2C substrates	Lumacaftor has the potential to induce CYP2B6, CYP2C8, CYP2C9, and CYP2C19; inhibition of CYP2C8 and CYP2C9 has also been observed in vitro. In vitro studies suggest that ivacaftor may also inhibit CYP2C9. Therefore, concomitant use of lumacaftor/ivacaftor with CYP2B6, CYP2C8, CYP2C9, and CYP2C19 substrates may alter the exposure of these substrates and should be monitored.
Lumacaftor/ ivacaftor	Anti-allergy and systemic corticosteroids	Lumacaftor/ivacaftor may decrease the exposure of montelukast and reduce its efficacy. No adjustment for montelukast is recommended but patients should be monitored closely. Lumacaftor/ivacaftor may also decrease the exposure of prednisone and methylprednisolone. Higher doses of these corticosteroids may be necessary.
Lumacaftor/ ivacaftor	Antibiotics	Concomitant use of lumacaftor/ivacaftor may decrease the levels of clarithromycin, erythromycin and telithromycin which may reduce their effectiveness. Consider an alternative to these antibiotics.
Lumacaftor/ ivacaftor	Antifungals	Concomitant use of lumacaftor/ivacaftor may decrease the levels of itraconazole, ketoconazole, posaconazole and voriconazole. Concomitant use is not recommended. Alternative therapy with fluconazole may be considered if appropriate.
Lumacaftor/ ivacaftor	Anti-inflammatory agents	Concomitant use of lumacaftor/ivacaftor may reduce the effectiveness of ibuprofen thereby necessitating a potentially higher dose of ibuprofen.
Lumacaftor/ ivacaftor	Antidepressants	Concomitant use of lumacaftor/ivacaftor may reduce the effectiveness of citalopram, escitalopram and sertraline. A higher dose of these antidepressants may be necessary in order to achieve the desired clinical effect.
Lumacaftor/ ivacaftor	Hormonal contraceptives	Lumacaftor/ivacaftor may reduce the effectiveness of all formulations of contraceptives. The hormonal contraceptives should not be relied upon as an effective method of contraception when co-administered with lumacaftor/ivacaftor. In addition, there was an increased incidence of menstrual abnormalities when used concomitantly. Avoid concomitant use unless the benefit outweighs the risks.
Lumacaftor/ ivacaftor	Oral hypoglycemics	Lumacaftor/ivacaftor may reduce the effectiveness of repaglinide and may alter the exposure of sulfonylureas. A dosage adjustment may be necessary when used concomitantly.
Lumacaftor/	Proton pump	Lumacaftor/ivacaftor may reduce the effectiveness of

Generic Name	Interacting Medication or Disease	Potential Result
ivacaftor	inhibitors, H2-blockers and antacids	omeprazole, esomeprazole and lansoprazole. In addition, it may alter the exposure of ranitidine. Dosage adjustments may be required for these agents in order to obtain the desired clinical effect. No dose adjustment is necessary for calcium carbonate antacid.
Lumacaftor/ ivacaftor	Warfarin	Exposure to warfarin may be altered by concomitant use of lumacaftor/ivacaftor. More frequent international normalized ratio (INR) monitoring may be necessary when co-administering these agents.

Dosage and Administration

Table 8. Dosing and Administration[3]

Generic Name	Adult Dose	Pediatric Dose	Availability
Lumacaftor/ ivacaftor	Cystic Fibrosis (homozygous for F508del): Tablet: initial; maintenance; maximum: Two tablets every 12 hours with fat-containing foods Dosage Adjustment for Patients with Moderate Hepatic Impairment (Child-Pugh Class B): Two tablets QAM and one tablet QPM with fat-containing foods Dosage Adjustment for Patients with Severe Hepatic Impairment (Child-Pugh Class C): Use with caution at a maximum dose of: One tablet every 12 hours with fat-containing foods Dosage Adjustment for Patients Taking CYP3A Inhibitors: No dosage adjustment is needed 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.	See adult dose. Safety and efficacy in children less than 12 years of age have not been established.	Tablet: 200 mg/125 mg

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
The Cystic Fibrosis Foundation: **Cystic Fibrosis Pulmonary Guidelines. Chronic Medications for Maintenance of Lung Health (2013)**[5]	· Chronic use of inhaled tobramycin is indicated for individuals 6 years of age and older with cystic fibrosis (CF), moderate to severe lung disease and *Pseudomonas aeruginosa* persistently present in cultures of the airways to improve lung function, quality of life and reduce exacerbations. · Chronic use of inhaled tobramycin is indicated for individuals 6 years of age and older with cystic fibrosis (CF), mild lung disease and *Pseudomonas aeruginosa* persistently present in cultures of the airways to reduce exacerbations. · Dornase alfa is recommended for individuals 6 years of age and older with moderate to severe lung disease to improve lung function, quality of life and reduce exacerbations. · Dornase alfa is recommended for individuals 6 years of age and older with mild lung disease to reduce exacerbations. · It is recommended to use chronic inhaled hypertonic saline to improve lung function and quality of life and reduce exacerbations in individuals 6 years of age and older. · For individuals with CF, 6 years of age and older, with *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic use of azithromycin to improve lung function and reduce exacerbations. · The Pulmonary Clinical Practice Guidelines Committee strongly recommends the chronic use of ivacaftor to improve lung function, quality of life and reduce exacerbations in CF individuals, 6 years of age and older, with at least one G551D CF transmembrane conductance regulator (*CFTR)* mutation. · Chronic use of inhaled aztreonam is indicated for individuals 6 years of age and older with moderate to severe lung disease and *P. aeruginosa* persistently present in cultures of the airways to improve lung function and quality of life. · Chronic use of inhaled aztreonam is indicated for individuals 6 years of age and older with mild lung disease and *P. aeruginosa* persistently present in cultures of the airways to improve lung function and quality of life. · For individuals with CF, between 6 and 17 years of age, with an FEV_1 ≥60% predicted, the CF Foundation recommends the chronic use of oral ibuprofen, at a peak plasma concentration of 50–100 µg/ml, to slow the loss of lung function.

Conclusions

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).

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DIVISION OF HEALTH CARE FINANCING AND POLICY
NEVADA MEDICAID
DRUG USE REVIEW (DUR) BOARD
PROPOSED PRIOR AUTHORIZATION CRITERIA

Orkambi® (lumacaftor/ivacaftor) is a covered benefit of Nevada Medicaid for recipients who meet the criteria for coverage.

1. Coverage and Limitations:
Authorization will be given if the following criteria are met and documented:

Requests for Orkambi® (lumacaftor/ivacaftor)

a. The recipient has a diagnosis of cystic fibrosis;
   AND
b. The recipient is 12 years of age or older;
   AND
c. The recipient is homozygous for the F508del mutation in the CFTR gene;
   AND
d. The requested dose is two tablets every 12 hours.

2. PA Guidelines:
Prior Authorization approvals will be given for a period of 1 year.

3. Quantity Limitations:
1 box/28 days (112 tablets/28 days)