PDL DRUG REVIEW

Proprietary Name: Orkambi®
Common Name: lumacaftor/ivacaftor
PDL Category: Cystic Fibrosis Agents

Comparable Products	Preferred Drug List Status
Kalydeco	Non-Preferred with Conditions

Summary

Indications and Usage: For the treatment of cystic fibrosis (CF) in patients 12 years of age 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. The safety and efficacy of Orkambi® have not been established in patients with CF other than those homozygous for the *F508del* mutation.

This is a pregnancy category B medication. The safety and efficacy of use in children under the age of 12 years have not been established.

Dosage Forms: Film-Coated Tablets: 200mg lumacaftor/125mg ivacaftor

Recommended Dosage: Take 2 tablets PO BID (Q12H) with fat-containing food (e.g. eggs, avocados, nuts, butter, peanut butter, cheese pizza, whole-milk dairy products, etc.).

Dose adjustments are not required with mild hepatic impairment; however, it is recommended to reduce the dose to 2 tablets in the AM and 1 tablet in the PM for those with moderate hepatic impairment. While studies have not been conducted in those with severe hepatic impairment, it is recommended to use Orkambi® with caution at a maximum dose of 1 tablet BID or less, after weighing the risks and benefits of treatment in this population. Furthermore, it is recommended that ALT, AST, and bilirubin levels be assessed prior to starting treatment, every 3 months during treatment for the first year, and annually thereafter. Dosing should be interrupted if AST or ALT levels are >5 times the upper limit of normal (ULN) if no bilirubin elevations. In addition, dosing should be interrupted if ALT or AST levels are >3 times ULN when associated with bilirubin elevations >2 times ULN.

While dose adjustments are not required in those with mild to moderate renal impairment, it is recommended to use Orkambi® with caution in those with severe renal impairment or end-stage renal disease (ESRD).

Drug Interactions: Numerous drug interactions are listed with Orkambi®. Warfarin & Digoxin: Monitor INR and digoxin levels. PPIs/H2 blockers/antacids: Orkambi® may decrease effectiveness and a dose adjustment may be needed. Oral hypoglycemics: Orkambi® may reduce effectiveness of repaglinide and alter the exposure of sulfonylureas. A dose adjustment may be required. Hormonal contraceptives: Orkambi® may decrease the effectiveness, including oral, injectable, transdermal, and implants. These should not be relied upon as an effective

method of contraception when co-administered with Orkambi®. Avoid the concomitant use unless the benefit outweighs the risks. Antidepressants & NSAIDs: Concomitant use of either with Orkambi® may decrease the effectiveness of citalopram, escitalopram, and sertraline, as well as ibuprofen. A higher antidepressant or ibuprofen dose may be needed. Antifungals and macrolide antibiotics: Concomitant use may decrease effectiveness of azole antifungals or macrolides. Consider alternative treatments. Systemic corticosteroids: Concomitant use may decrease effectiveness of prednisone/methylprednisolone. Dose adjustments may be required.

CYP450 System: Concomitant use of Orkambi® is not recommended with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index (e.g. benzodiazepines or immunosuppressants). Concomitant use of Orkambi® with CYP2B6, CYP2C8, CYP2C9, and CYP2C19 substrates may alter the exposure of these substrates. Concomitant use of Orkambi® with strong CYP3A4 inducers (e.g. rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John 's wort) is not recommended. While dose adjustments are not required when CYP3A4 inhibitors are initiated in patients currently taking Orkambi®, dose adjustments are needed when initiating Orkambi® in patients taking strong CYP3A inhibitors. The Orkambi® dose should be reduced to 1 tablet daily for the first week, then continue with normal maintenance dose.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Orkambi®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same or that the active drug was less than its comparator.* The most frequently reported adverse events included dyspnea (5%), nasopharyngitis (2%), nausea (5%), diarrhea (4%), upper respiratory tract infection (5%), fatigue (1%), respiration abnormal (3%), blood creatinine phosphokinase increased (2%), rash (5%), flatulence (4%), rhinorrhea (2%), and influenza (3%).

Menstrual abnormalities occurred more with Orkambi® vs placebo (10% vs 2%). Furthermore these occurred more in the subset of females treated with Orkambi® who were using hormonal contraceptives (27%) as compared to those not using hormonal contraceptives (3%).

Serious liver-related adverse events related to elevated transaminases have been reported in patients with CF taking Orkambi®, thus it is recommended that ALT, AST, and bilirubin levels should be monitored.

Clinical experience in patients with % predicted FEV1 <40 is limited. Therefore, it is recommended to perform additional monitoring in this population when initiating therapy.

It is recommended to obtain baseline and follow-up ophthalmological exams in the pediatric population starting Orkambi®, as cases of non-congenital lens opacities have been reported in pediatric patients treated with ivacaftor.

Contraindications: There are currently none listed in the prescribing information.

Manufacturer: Vertex

Analysis: Orkambi® is a combination product that contains the active ingredients lumacaftor and ivacaftor. Cystic fibrosis transmembrane conductance regulator (CFTR) protein is a chloride channel at the surface of epithelial cells in many organs. The *F508del* mutation results in protein misfolding, causing a defect in cellular processing and trafficking that targets the protein for degradation and thus reduces the quantity of CFTR at the cell surface. Lumacaftor acts by improving the conformation stability of F508del-CFTR, which results 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 of the CFTR protein on the cell surface.

Dose ranging and 2 confirmatory randomized, double-blind, placebo-controlled studies were performed to assess the safety and efficacy of Orkambi®. The two confirmatory trials included patients with CF (N=1108) who were homozygous for the *F508del* mutation in the CFTR gene and who: were ≥12 years of age and with percent of predicated forced expiratory volume at one second (ppFEV1) at screening ranging from 40-90. Those with a history

of colonization with organisms such as *Burkholderia cenocepacia, Burkholderia dolosa*, or *Mycobacterium abscessus*, or who had ≥3 abnormal liver function tests were excluded. The primary efficacy endpoint in both studies was the change in lung function as determined by absolute change from baseline in ppFEV1 at week 24.

Results suggested that in both trials Orkambi® resulted in statistically significant improvement in ppFEV1, with the treatment difference between placebo for the mean absolute change from baseline at week 24 being 2.6% points in trial 1 (p=0.0003) and 3% points in trial 2 (p<0.0001). Note that these results were assessed as the average of the treatment effects at week 16 and week 24. Key secondary outcomes included relative change in ppFEV1 at week 24, 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 25, and the number of pulmonary exacerbations through week 24. The table below includes results of these secondary outcomes.

	Trial 1		Trial 2	
	placebo (N=184)	Orkambi® (N=182)	placebo (N=187)	Orkambi® (N=187)
Treatment difference in: Relative change in ppFEV1 at week 24	-	4.3% (p=0.0006)	-	5.4% (p<0.0001)
Absolute change in BMI at week 24 (kg/m^2)	-	0.1	-	0.4 (p=0.0001)
Treatment difference: Absolute change in CFQ-R Respiratory Domain score	-	1.5 points	-	2.9 points
Proportion with≥5% relative change in ppFEV1 at week 24	22%	37% (odds ratio 2.1)	23%	41% (odds ratio 2.4)
Number of pulmonary exacerbations through week 24 (# events)	112	73	139	79

Place in Therapy: Orkambi® is a new combination product that contains the active ingredients ivacaftor and lumacaftor. It is approved for the treatment of CF in those who are homozygous for the *F508del* mutation in the *CFTR* gene. One noted reference source recommends treatment with lumacaftor/ivacaftor (grade 2B) for all CF patients' ≥12 years with CF who are homozygous for F508del, but with consideration for potential drug interactions.

It is recommended that Orkambi® remain non-preferred and require clinical prior authorization.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred with Conditions**
- ☐ **Preferred with Conditions**

References

[1] Orkambi [package insert]. Boston, MA: Vertex Pharmaceuticals, Inc; 2015.

[2] UpToDate desktop version. Cystic Fibrosis: Overview of the treatment of lung disease. Accessed August 2015.