CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	June 30, 2015
Reviewer(s):	Jasminder Kumar, Pharm.D., Division of Risk Management (DRISK)
Acting Team Leader:	Jamie Wilkins Parker, Pharm.D., DRISK
Acting Deputy Director:	Reema Mehta, Pharm.D., M.P.H., DRISK
Subject:	Review evaluates if a REMS is needed for Orkambi™
Drug Name:	Orkambi™ (lumacaftor 200mg /ivacaftor 125mg), fixed dose combination (FDC)
Therapeutic Class:	cystic fibrosis transmembrane conductance regulator (CFTR) (b) (4) and potentiator combination
Dosage form and route:	Oral tablet
Application Type/Number:	NDA 206038
Applicant/Sponsor:	Vertex Pharmaceuticals Incorporated
OSE RCM #:	2014-2323

*** This document contains proprietary and confidential information that should not be released to the public. ***

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1 INTRODUCTION

The purpose of this review is to provide the Division of Risk Management's (DRISK) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) fixed dose combination (FDC) of Orkambi (lumacaftor/ivacaftor). A new drug application (NDA 206038) for Orkambi was received by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) from Vertex Pharmaceuticals, Inc. on November 5, 2014. Lumacaftor is the NME component of the application. Ivacaftor (Kalydeco, NDA 203188) was approved on January 31, 2012 for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have one of the following mutations in the cystic fibrosis conductance regulator (*CFTR*) gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S125 5P, S549N, or S549R.* The Sponsor did not submit a proposed REMS.

1.1 PRODUCT BACKGROUND

Orkambi (lumacaftor/ivacaftor) is a fixed dose cystic fibrosis transmembrane conductance regulator (*CFTR)* combination (b) (4) and potentiator with a proposed indication for the treatment of CF in patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene. There are currently no other FDA-approved products available for CF patients homozygous for the *F508del* mutation that specifically target the disease, rather than target the symptoms associated with CF. If the patient's genotype is unknown, an FDA-approved CF mutation test should be used to detect the presence of the *F508del* mutation on both alleles of the *CFTR* gene. The CFTR protein is a chloride channel present at the surface of epithelial cells in multiple organs. Lumacaftor (LUM) is a CFTR (b) (4) that acts directly on F508del-CFTR to improve its cellular processing and trafficking, thereby increasing the quantity of function CFTR at the cell surface; Ivacaftor (IVA) 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. Thus, the combination of the two components increases the quantity and function of F508del-CFTR at the cell surface, resulting in increased chloride ion transport. Orkambi will be available as an oral tablet. The proposed dosing regimen is two tablets (each containing LUM 200mg/IVA 125mg), taken orally every 12 hours with fat-containing food.

1.2 DISEASE BACKGROUND

CF is an autosomal recessive genetic disease that results from a dysfunction in the CFTR and affects approximately 30,000 individuals in the United States. It is more prominently seen in Caucasians. Over 1,800 mutations have been identified, with the most common identified as *F508del*, which is found in about 90% of patients. The CFTR protein functions as a channel for the movement of chloride ions in and out of the cells and is expressed primarily at the apical plasma membrane of secretory epithelia in the airway, intestine, pancreas, and other tissues. These mutations in the CFTR gene result in abnormal airway secretions, chronic endobronchial infection, and progressive airway obstruction. In the classic presentation of CF, the patient will have symptoms of chronic sinus and pulmonary infections, pancreatic insufficiency, and elevated sweat chloride. However, in non-classic CF, patients will maintain pancreatic function. In addition, more than 10% of people with CF have liver disease, a number that may increase as people with CF live longer. Cystic fibrosis liver disease is the third most frequent cause of death

in CF after respiratory and transplantation complications and accounts for 2.3% of all mortality. [1] With current care, affected individuals with CF have a life expectancy of approximately 40 years of age.[2,3]

Although there is no cure, historically, intravenous antibiotics have been the mainstay of CF therapy, but a new focus has shifted to optimizing nutrition status and promoting effective pulmonary clearance. Table 1 below describes the recommended treatment regimens used for continuing chronic therapies for maintenance of lung health. Kalydeco (ivacaftor), approved on January 31, 2012, for people ages 6 and older with the *G551D* mutation, is the first drug that focuses on treating the basic defect of the disease, the CFTR dysfunction, rather than the effects of diminished CFTR function.

(b) (4) target the *F508del* misprocessing, whereas potentiators are used to restore cAMP-dependent chloride channel activity. Traditional CF treatment options, including antibiotics, anti-inflammatory agents, mucolytics, pancreatic enzyme replacement, treat disease manifestations. On the other hand, (b) (4) and potentiators, like Orkambi, may help to correct the underlying CFTR anion channel defect in this disease.[4]

Table 1. Abridged Cystic Fibrosis Pulmonary Guidelines[5]:

Treatment	Recommendation	Recommendation
Inhaled tobramycin—moderate to severe disease*	For individuals with CF, 6 years of age and older, with moderate to severe lung disease and Pseudomonas aeruginosa persistently present in cultures of the airways, the CF Foundation strongly recommends the chronic use of inhaled tobramycin to improve lung function and quality of life, and reduce exacerbations.	A
Inhaled tobramycin – mild disease*	For individuals with CF, 6 years of age and older, with mild lung disease and P. aeruginosa persistently present in cultures of the airways, the CF Foundation recommends the chronic use of inhaled tobramycin to reduce exacerbations.	B
Dornase alfa—moderate to severe disease*	For individuals with CF, 6 years of age and older, with moderate to severe lung disease, the CF Foundation strongly recommends the chronic use of dornase alfa to improve lung function, improve the quality of life, and reduce exacerbations.	A
Dornase alfa—mild disease*	For individuals with CF, 6 years of age and older, with asymptomatic or mild lung disease, the CF Foundation recommends the chronic use of dornase alfa to improve lung function and reduce exacerbations.	B

[1] Cystic Fibrosis Foundation. CF Care Guidelines - Nutrition/GI. Updated 7/19/12.

[2] Farrell PM, Rosenstein BJ, White TB, et al. Guidelines for Diagnosis of Cystic Fibrosis in Newborns through Older Adults: Cystic Fibrosis Foundation Consensus Report. *J Pediatr*. 2008; 153:S4-S14.

[3] Cystic Fibrosis Foundation Patient Registry, 2013 Annual Data Report. Bethesda, MD: Cystic Fibrosis Foundation.

(b) (4)

[5] Mogazyzel PJ, Naureckas ET, Robinson KA. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2013 Apr 1;187(7):680-9.

Treatment	Recommendation	Recommendation
Inhaled hypertonic saline	For individuals with CF, 6 years of age and older, the CF Foundation recommends the chronic use of inhaled hypertonic saline to improve lung function and quality of life and reduce exacerbations.	B
Azithromycin with P. aeruginosa	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.	B
Ivacaftor**	For individuals with CF, 6 years of age and older, with at least one G551D CFTR mutation, the Pulmonary Clinical Practice Guidelines Committee strongly recommends the chronic use of ivacaftor to improve lung function and quality of life and reduce exacerbations.	A
Inhaled aztreonam—moderate to severe disease*	For individuals with CF, 6 years of age and older, with moderate to severe lung disease and Pseudomonas aeruginosa persistently present in cultures of the airways, the CF Foundation strongly recommends the chronic use of inhaled aztreonam to improve lung function and quality of life.	A
Inhaled aztreonam—mild disease†	For individuals with CF, 6 years of age and older, with mild lung disease and P. aeruginosa persistently present in cultures of the airways, the CF Foundation recommends the chronic use of inhaled aztreonam to improve lung function and quality of life.	B
Chronic use of ibuprofen (age , 18 yr)	For individuals with CF, between 6 and 17 years of age, with an FEV1 > 60% predicted, the CF Foundation recommends the chronic use of oral ibuprofen, at a peak plasma concentration of 50–100 mg/ml, to slow the loss of lung function.	B
Azithromycin without P. aeruginosa	For individuals with CF, 6 years of age and older, without P. aeruginosa persistently present in cultures of the airways, the CF Foundation recommends the chronic use of azithromycin should be considered to reduce exacerbations.	C

* Severity of lung disease is defined by FEV1% predicted as follows: normal, .90% predicted; mildly impaired, 70–89% predicted; moderately impaired, 40–69% predicted; and severely impaired, ,40% predicted.
** CF Foundation personnel did not participate in any activity related to ivacaftor.

1.3 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 206-038 relevant to this review:

December 7, 2012: The Sponsor was granted breakthrough designation.

November 5, 2014: The Agency received a NDA submission from Vertex Pharmaceuticals, Inc. The Sponsor did not submit a proposed REMS.

December 31, 2014: The Agency determined the review classification for this application is Priority

February 19, 2015: A Mid-Cycle meeting was held between the Agency and the Sponsor via teleconference. The Agency informed the Sponsor that based on the currently available data a REMS was not needed for Orkambi.

May 12, 2015: A Pulmonary-Allergy Advisory Committee Meeting was held to discuss the safety and efficacy of Orkambi. The committee voted 12 to 1 in favor of approval of Orkambi, 400mg/250mg FDC, administered twice daily in patients with CF homozygous for the F508del mutation in the CFTR gene.

2 MATERIALS REVIEWED

The following is a list of materials that informed our review:

- Vertex Pharmaceuticals, Inc. Summary of Clinical Safety for Orkambi (lumacaftor/ivacaftor), received November 5, 2014.
- Vertex Pharmaceuticals, Inc. Summary of Clinical Efficacy for Orkambi (lumacaftor/ivacaftor), received November 5, 2014.
- Vertex Pharmaceuticals, Inc. Lumacaftor/ivacaftor Combination Therapy Safety Update (eCTD Sequence 0010), received February 3, 2015.
- Vertex Pharmaceuticals, Inc. Proposed Prescribing Information for Orkambi (lumacaftor/ivacaftor) (eCTD Sequence 0018), received May 27, 2015.
- Lim R. DPARP. Clinical Review for Orkambi (lumacaftor/ivacaftor), NDA 206038, dated June 2, 2015.

3 REVIEW FINDINGS FOR ORKAMBI

3.1 OVERVIEW OF CLINICAL PROGRAM AND EFFICACY

The clinical program for the LUM/IVA FDC was comprised of two replicate, 24-week, double-blind, randomized, multi-center, placebo-controlled Phase 3 trials involving 1108 subjects with CF, 12 years and older, who are homozygous for the *F508del* mutation in the *CFTR* gene (Study 103 and 104). Additional studies conducted include a Phase 2 multi-cohort dose-ranging study (Study 102) and an ongoing uncontrolled extension study (Study 105).

In the two replicate efficacy trials (103 and 104), patients were randomized 1:1:1 to receive either LUM 600mg once daily/ IVA 250mg every 12 hours, LUM 400mg every 12 hours/IVA 200mg every 12 hours, or placebo. The primary efficacy endpoint in all trials was the absolute change from baseline in percent predicted FEV_1 ($ppFEV_1$) at Week 24, assessed as the average treatment effect at Week 16 and Week 24. Key secondary efficacy endpoints included: relative change from baseline in $ppFEV_1$ at Week 24, assessed as the average treatment effect at Week 14 and Week 24; absolute change from baseline in body mass index (BMI) at Week 24; absolute change from baseline in the Cystic Fibrosis Questionnaire-Revised respiratory domain score at Week 24; response defined as $\geq$5% increase in average relative change from baseline in $ppFEV_1$ at Week 16 and Week 24; and number of pulmonary exacerbations through Week 24.

Study 103 (VX12-809-103) included 549 patients in the safety set. The least squares (LS)-mean average absolute change from baseline in in $ppFEV_1$ at Week 24 (assessed as the average treatment effect at Week 16 and Week 24) was greater for the LUM 600mg daily/IVA 250mg every 12 hours group (3.59%) and the LUM 400mg/IVA 250mg every 12 hours group (2.16%) compared to placebo (-0.44%). The LS mean treatment difference for the LUM 600mg daily/IVA 250mg every 12 hours group vs. placebo was 4.03% (95% CI: 2.62, 5.44; $p<0.0001$). The LS-mean treatment difference for the LUM 400mg/IVA 250mg every 12 hours vs. placebo was 2.60% (95% CI: 1.18, 4.01; $p=0.0003$).

Study 104 (VX12-809-104) included 559 patients in the safety set. The LS-mean average absolute change from baseline in $ppFEV_1$ at Week 24 (assessed as the average treatment effect at

Week 16 and Week 24) was greater for the LUM 600mg daily/IVA 250mg every 12 hours group (2.46%) and the LUM 400mg/IVA 250mg every 12 hours group (2.85%) compared to placebo (-0.15%). The LS mean treatment difference for the LUM 600mg daily/IVA 250mg every 12 hours group vs. placebo was 2.62% (95% CI: 1.18, 4.06; P<0.0004). The LS-mean treatment difference for the LUM 400mg/IVA 250mg every 12 hours vs. placebo was 3.00% (95% CI: 1.56, 4.44; P<0.0001).

Orkambi was also studied in a multicenter, double-blind, randomized, placebo-controlled, Phase 2 trial (Study 102) in 125 patients with CF aged 18 years and older who had a ppFEV of 40 to 90. Eligible subjects had the *F508del* mutation on 1 allele plus a second allele with a mutation predicted to result in the lack of CFTR production or a CFTR that is not responsive to ivacaftor in vitro (**heterozygous** for the *F508del* mutation). Subjects were randomized 1:1 to receive either LUM 400mg/IVA 250mg every 12 hours or placebo for 8 weeks. The primary endpoint was change from baseline at Day 56 in $ppFEV_1$. Treatment with Orkambi did not result in significant improvement in ppFEV1 relative to placebo (treatment difference 0.60 (p=0.5978)) or secondary endpoints including relative change in $ppFEV_1$, BMI, and weight.

Study 105 is an ongoing, Phase 3, multicenter, parallel-group, 2-part rollover study in patients with CF, which included patients that completed 24 weeks of treatment in either Study 103 or 104, or patients that completed 56 days of treatment in Cohort 4 of Study 102. This study is designed to evaluate the safety and efficacy of long-term (96 weeks) of Orkambi therapy. An ad hoc efficacy analyses was performed and patients who received active treatment in Studies 103 and 104 had improvements in $ppFEV_1$ from Day 15, through subsequent visits up to and including Week 24 of Studies 103 and 104 that were sustained through all visits in Study 105. Patients who received placebo in Studies 103 and 104 had improvements in $ppFEV_1$ upon receiving active treatment in Study 105 (2.62 percentage points absolute and 4.93% relative change compared to baseline in Trial 1 or Trial 2). Improvements in BMI and weight up were also seen in patients who received active treatment in Studies 103 and 104 but the magnitude of improvement was smaller for the patients who received placebo/LUM 600mg daily/IVA 250mg every 12 hours.

Overall, the clinical reviewer determined that Orkambi demonstrated statistically significant treatment differences in favor of active treatment for the primary endpoint of absolute change from baseline in ppFEV1 at Week 24 (assessed as the average treatment effect at Week 16 and at Week 24) at both dosing regimens. However, the results were modest in benefit and did not distinguish between the two regimens studied in Phase 3. For secondary endpoints, there was no consistent BMI effect across studies, and the number of pulmonary exacerbations was only nominally statistically significant due to hierarchy.[6] However, Orkambi was not effective in patients with CF heterozygous for the *F508del* mutation in the CFTR gene and is not recommended for use in this population.

3.2 SAFETY CONCERNS

For the purpose of this review, serious adverse events (SAEs) associated with Orkambi are defined by the regulatory definition of a serious outcome, such as death, a life-threatening

[6] Lim R. DPARP. Clinical Review for Orkambi, dated June 2, 2015.

reaction, or hospitalization (among other outcomes). Severe adverse events associated with Orkambi are defined as Grade 3-4 using the Sponsor's Toxicity Grading Scale. During the clinical program, 2 grading scales were used for scoring adverse event severity: the Common Terminology Criteria for Adverse Events (CTCAE) grading scale and the FDA's "toxicity grading scale for health adults and adolescent volunteers enrolled in preventative vaccine clinical trials" (Vaccine Toxicity Grading Scale).

Common Adverse events

The overall safety population included a total of 1108 patients with CF 12 years of age and older who are homozygous for the F508del mutation in the CFTR gene and who received at least one dose of the study drug in 2 double-blind, placebo-controlled, Phase 3 clinical trials. A total of 483 (43.59%) subjects had at least 1 adverse event considered related or possibly related to the drug. Overall, the most common adverse events (at least 15% incidence in any treatment group) were infective pulmonary exacerbation of CF, cough, headache, and sputum increase. The most frequently reported adverse reactions seen with Orkambi (occurring in ≥10% of patients) were dyspnea, hemoptysis, nausea, and diarrhea. The incidence of adverse events leading to study drug discontinuation was higher in the LUM/IVA group (4.2%) than the placebo group (1.6%).

3.2.1 Serious Adverse Events (SAEs)

A total of 254 (22.92%) subjects had at least 1 SAE. The incidence of SAEs was lower in the LUM/IVA group (20.1%) than the placebo group (28.6%). The incidence of adverse events considered by the investigator to be related to the study drug was similar between LUM/IVA (3.0%) and placebo (2.2%).

No deaths occurred during the placebo controlled Phase 3 studies. One subject in Study 105 had an SAE (infective pulmonary exacerbation of cystic fibrosis) with fatal outcome approximately 1 year after starting study drug, but the event was considered to be unrelated to study drug by the investigator. DPARP clinical reviewer noted based on available clinical information, causality cannot be assessed.[7]

3.2.2 Severe Adverse Events

A lower percentage of subjects had Grade 3/4 adverse events in the total pooled LUM/IVA group (13.8%), compared with placebo (15.9%). The incidence of severe adverse events was lower in the LUM 400 mg/IVA 250 mg every 12 hours group (11.9%) compared with the LUM 600 mg daily/IVA 250 mg every 12 hours group (15.2%) and placebo (15.1%). Most of the Grade 3 or 4 adverse events were respiratory and gastrointestinal events. Grade 3 or 4 AEs that had an incidence of at least 1% in any treatment group included: infective pulmonary exacerbation of CF (7.8% in the placebo group, 4.3% in the LUM 400 mg/IVA 250 mg every 12 hours group, and 7.3% in the LUM 600 mg daily/ IVA 250 mg every 12 hours group), headache (0.5% in the placebo group, 0.5% in the LUM 400 mg/IVA 250 mg every 12 hours group, and 1.1% in the LUM 600 mg daily/IVA 250 mg every 12 hours group), and increased blood creatine phosphokinase (0.3% in placebo, 1.1% in the LUM 400 mg/IVA 250 mg every 12 hours group, and 0% in the LUM 600 mg daily/IVA 250 mg every 12 hours group.

[7] Lim R. DPARP. Clinical Review for Orkambi, dated June 2, 2015.

Five subjects had life-threatening (Grade 4) adverse events: 3 subjects in the placebo group (acute renal failure; metastatic colon cancer; and suicide attempt), 1 subject in the LUM 600 mg daily/ IVA 250 mg every 12 hours group (cholestasis, hepatitis, and hematoma), and 1 subject in the LUM 400 mg/IVA 250 mg every 12 hours group (hemoptysis). All cases, except case of suicide attempt and hemoptysis, were considered unlikely related to the study drug. The SAE of suicide attempt and hemoptysis were considered possibly related and related to the study drug, respectively.

3.2.3 Hepatobiliary Adverse Events

Liver-related safety concerns related to IVA alone, a component of Orkambi, led to further analysis of the potential liver-related risks with Orkambi.[8] The FDA-approved labeling for IVA currently includes elevated transaminases (ALT or AST) in the Warnings and Precautions section and Orkambi will also contain a similar Warning and Precautions.

In the pooled placebo-controlled studies, 5.7% of patients had elevated transaminases or hepatobiliary disorder-related adverse events in the total LUM/IVA group compared with 5.4% of patients in the placebo group. Among patients with SAE's of elevated transaminases or hepatobiliary disorders, 4 subjects in total in the LUM/IVA group discontinued treatment. The maximum transaminase (ALT or AST) level >8, >5, and >3x the ULN were 0.8%, 2.0%, and 5.2% (ALT), and 0.5%, 1.9%, and 5.1% (AST) in both the LUM/IVA and placebo groups. Serious adverse reactions occurring in at least 0.5% of subjects on LUM/IVA and greater than placebo were hepatobiliary events, including 4 reported as transaminase elevations, 2 as cholestatic hepatitis, and 1 as hepatic encephalopathy. Three of these cases were also associated with a concurrent elevation of bilirubin. When examining the patients with ALT or AST elevations >3x ULN and with total bilirubin elevations >2x ULN, there were three cases in the LUM/IVA groups and none in the placebo group. Generally, liver transaminases returned to baseline on discontinuation or treatment interruption. The clinical reviewer suggests that although the numbers are small, the SAE and discontinuation data suggest that LUM/IVA use may be associated with increased risk of liver toxicity. However, this is based on a relatively small number of events in a patient population prone to liver disease.[8]

Among 7 patients with pre-existing cirrhosis and/or portal hypertension who received Orkambi, worsening liver function with increased ALT, AST, bilirubin, and hepatic encephalopathy was observed in one patient. The event occurred within 5 days of the start of dosing and resolved following discontinuation of Orkambi. Although this case resolved following discontinuation, the event could not be excluded.

4 DISCUSSION

Based on results of the Phase 3 trials, Orkambi (lumacaftor/ivacaftor) was found to be efficacious versus placebo with an acceptable safety profile for patients homozygous to the *F508del* gene. The most important safety concern associated with Orkambi is hepatobiliary events, due to liver-related safety concerns seen with IVA alone. Orkambi appears to be associated with liver abnormalities, including elevated transaminases in some patients, though elevated liver transaminases were reversible with dose reduction or discontinuation, and there have been no hepatic adverse events that resulted in death. Although there were cases of liver

[8] Chowdhury B. DPARP. Division Director Summary Review for Orkambi, dated June 25, 2015.

abnormalities, the observed safety profile was consistent with the disease state and the risks seen were reversible with discontinuation or interruption of study drug. The most likely prescribers of Orkambi are specialists who are familiar with the management of CF, frequently monitor patients, and understand the risks of treatment. Therefore, with the lower incidence of serious and non-serious safety issues compared to placebo, as well as Warnings and Precautions adequately communicated through the labeling, a REMS is not warranted at this time to ensure the benefits of this drug outweigh its risks.

The FDC tablet offers a comparable safety profile (including hepatic warnings, hepatobiliary events, and monitoring before and during treatment) to one of its monocomponents, Kalydeco (IVA), which is also used to treat patients with CF (albeit patients with a different genetic profile), is prescribed by a similar prescriber population, and currently does not require a REMS.

Therefore, based on the currently available data, DRISK does not recommend a REMS as necessary to ensure the benefits of Orkambi outweigh the risks. CF is a rare disease that affects about 30,000 individuals in the United States and currently has no cure. The Agency has designated Orkambi as a breakthrough therapy, and there are no Boxed Warnings under consideration. The proposed Warnings and Precautions section of the Package Insert Labeling for Orkambi includes use in patients with advanced liver disease, hepatobiliary events (with monitoring before and during treatment). In addition, the Orkambi label cautions use in patients with advanced liver disease, and recommends use in this patient population only if benefits are considered to outweigh the risks.

5 CONCLUSION AND RECOMMENDATIONS

In conclusion, risk mitigation measures beyond professional labeling are not warranted for Orkambi (lumacaftor/ivacaftor). The serious risk of hepatobiliary events and use in patients with advance liver disease will be included in the Warnings and Precautions section of the labeling. Based on the currently available data, the benefit-risk profile for Orkambi is acceptable for the treatment of CF in patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene and a REMS is not warranted at this time.

Should DPARP have any concerns or questions, or feel that a REMS may be warranted for this product, or if new safety information becomes available, please send a consult to DRISK.

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/s/

JASMINDER N KUMAR
06/30/2015

REEMA J MEHTA
07/01/2015
I concur.