

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210491Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	210491
PDUFA Goal Date	February 28, 2018
OSE RCM #	2017-1297
Reviewer Name(s)	Bob Pratt, Pharm.D.
Team Leader	Donella Fitzgerald, Pharm.D.
Deputy Division Director	Jamie Wilkins Parker, Pharm.D.
Review Completion Date	February 5, 2018
Subject	Evaluation of need for a REMS
Established Name	Tezacaftor/Ivacaftor
Trade Name	Symdeko™
Name of Applicant	Vertex Pharmaceuticals Inc.
Therapeutic Class	CFTR corrector/potentiator
Formulation(s)	Tezacaftor/Ivacaftor 100 mg/150 mg and Ivacaftor 150 mg
Dosing Regimen	One tablet (containing tezacaftor/ivacaftor 100 mg/150 mg) in the morning and one tablet (containing ivacaftor 150 mg) in the evening

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EXECUTIVE SUMMARY

This review by the Division of Risk Management evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Symdeko™ (tezacaftor/ivacaftor) is necessary to ensure the benefits of this product outweigh the risks. Vertex Pharmaceuticals submitted a New Drug Application (NDA 210491) on June 28, 2017, with the proposed indication for the treatment of patients with cystic fibrosis age 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor (TEZ/IVA) based on in vitro data and/or clinical evidence.

Tezacaftor is the NME component of the drug combination; ivacaftor was approved in 2012 and is currently indicated for the treatment of cystic fibrosis in patients age 2 years and older who have one mutation in the CFTR gene that is responsive to ivacaftor potentiation. Ivacaftor is also approved for use in combination with the CFTR modulator lumacaftor. The most important safety concerns associated with TEZ/IVA are elevated liver transaminases and cataracts. The Applicant submitted a risk management plan that proposes routine pharmacovigilance and use of the product labeling.

Cystic fibrosis (CF) is a serious, progressive, multisystem, life-shortening, autosomal recessive disease that is caused by reduced quantity and/or function of the CFTR protein due to mutations in the gene. TEZ/IVA showed substantial evidence of efficacy in the treatment of CF patients age 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the CFTR gene responsive to the treatment. Based on the currently available data, there is an absence of new safety concerns unique to the TEZ/IVA combination compared with the use of ivacaftor as a single-agent treatment for CF or the use of ivacaftor in combination with lumacaftor. DRISK recommends that a REMS is not necessary to ensure the benefits of TEZ/IVA outweigh the risks.

1 Introduction

This review by the Division of Risk Management evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Symdeko™ (tezacaftor/ivacaftor) is necessary to ensure the benefits of this product outweigh its risks. Vertex Pharmaceuticals (Vertex) submitted a New Drug Application (NDA 210491) on June 28, 2017, with the proposed indication for the treatment of patients with cystic fibrosis (CF) age 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor (TEZ/IVA) based on in vitro data and/or clinical evidence. This application is under review in the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). The Applicant submitted a risk management plan that proposes routine pharmacovigilance and use of the product labeling.

2 Background

2.1 PRODUCT INFORMATION

TEZ/IVA is a fixed dose combination CFTR corrector and potentiator with the proposed indication for the treatment of patients with cystic fibrosis age 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the CFTR gene that is responsive to TEZ/IVA. The CFTR

protein is a chloride channel that helps regulate salt and water absorption and secretion across epithelial cells in multiple organs. The F508del mutation interferes with CFTR protein folding and channel gating. Tezacaftor, the NME component of the drug combination^a, is a CFTR corrector that acts on the defective CFTR gene product to improve its cellular processing and trafficking, thereby increasing the amount of CFTR at the cell surface. Ivacaftor is currently approved for the treatment of cystic fibrosis in patients age 2 years and older who have one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data. Ivacaftor facilitates increased chloride transport by potentiating the channel open probability (or gating) of CFTR protein located at the cell surface. Thus, the combination of tezacaftor and ivacaftor intends to increase the quantity and function of CFTR at the cell surface, resulting in increased chloride ion transport. Ivacaftor is also approved for use in combination with the CFTR modulator lumacaftor. The combination of lumacaftor/ivacaftor has a similar mechanism of action as TEZ/IVA and is indicated for patients who are homozygous for the F508del mutation. However, lumacaftor is a strong inducer of CYP3A and ivacaftor is a CYP3A substrate, resulting in a drug-drug interaction that reduces ivacaftor exposure and limits clinical efficacy. The TEZ/IVA combination is without this drug interaction.

Symdeko™ is a chronic therapy^b supplied as a TEZ/IVA fixed dose combination tablet containing 100 mg of tezacaftor and 150 mg of ivacaftor that is taken in the morning, and a tablet containing 150 mg of ivacaftor that is taken in the evening. Tezacaftor in combination with ivacaftor received Breakthrough Therapy designation on January 28, 2014 and received orphan product designation on June 15, 2017. TEZ/IVA is not currently approved in any other country.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 210491 relevant to this review:

- 1/28/2014: Breakthrough Therapy designation granted for the treatment of cystic fibrosis patients who are homozygous for the F508del mutation in the CFTR
- 6/15/2017: Orphan product designation granted for the treatment of cystic fibrosis
- 6/28/2017: NDA 210491 submission for the treatment of cystic fibrosis
- 11/2/2017: A post mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that no major safety concerns have been identified at this time and currently, there is no need for a REMS.
- 12/19/2017: A late-cycle meeting was held between the Agency and the Applicant. There was no discussion related to the need for a REMS.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

^a FDAAA factor (F): Whether the drug is a new molecular entity.

^b FDAAA factor (D): The expected or actual duration of treatment with the drug.

Cystic fibrosis is an autosomal recessive genetic disease resulting from a defective CFTR protein that affects approximately 30,000 individuals in the U.S.^c Over 2,000 mutations in the CFTR gene have been identified with the most common mutation identified as F508del, which is found in over 70% of U.S. patients.¹ Deranged transport of chloride and/or other CFTR-affected ions, such as sodium and bicarbonate, leads to thick, viscous secretions in the lungs, pancreas, liver, intestine, and reproductive tract; CF patients can develop multisystem disease involving several or all of these organs. Typical pulmonary manifestations include chronic airway obstruction caused by viscous respiratory secretions, chronic pulmonary infection, and chronic inflammation, which ultimately advances to the stage of irreversible bronchiectasis and progressive respiratory failure. Patients with CF can also experience chronic sinus infections, pancreatic insufficiency, pancreatitis, malnutrition, poor growth, CF-related diabetes, distal intestinal obstructive syndrome, focal biliary cirrhosis, cholelithiasis, infertility, and other clinical manifestations.² Obstructive lung disease is the primary cause of morbidity and mortality. The median age at death was 29.6 years for the 373 people in the Cystic Fibrosis Foundation Registry reported to have died in 2016. Over the 5-year period of 2012 to 2016, the median predicted survival age was 42.7 years.^{3,d}

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The Cystic Fibrosis Foundation provides multiple clinical care guidelines^e from the medical literature for the management of CF, including guidelines that address nutrition and the use of pancreatic enzymes; the treatment of pulmonary exacerbations and chronic infections, and the use of pulmonary maintenance medications; infection prevention and control; treatment of CF-related diabetes; management of hepatic and biliary disease; and the treatment of CF-related bone disease, among other guidelines.

Current molecular therapy for cystic fibrosis includes the CFTR modulators ivacaftor and lumacaftor. Ivacaftor is approved for single-agent use and use in combination with lumacaftor. These agents act by improving function of the defective CFTR protein. The indications and efficacy of these drugs depend on the CFTR mutation in the individual patient. Ivacaftor was designed to treat patients who have a G551D mutation in at least one of their CFTR genes. The G551D mutation is a gating mutation that impairs the regulated opening of the ion channel formed by the CFTR protein. Subsequent clinical trials and laboratory studies have led to expansion of the list of CFTR mutations responsive to ivacaftor such that the product labeling currently shows 38 mutations as being responsive. For individuals who are homozygous for the F508del mutation, treatment with the combination of lumacaftor and ivacaftor (Orkambi[®]) is indicated for CF patients age six years and older. Lumacaftor partially corrects misfolding of the CFTR protein and improves its conformational stability, resulting in increased processing and trafficking of mature protein to the cell surface, while ivacaftor improves the gating abnormality. Neither drug is effective when used as single-agent therapy for patients who are F508del homozygous.^{4,5}

4 Benefit Assessment

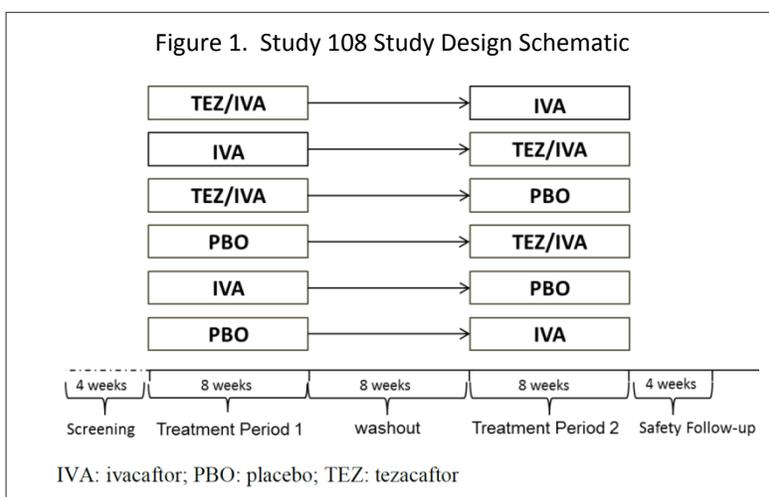
^c FDA factor (A): The estimated size of the population likely to use the drug involved.

^d FDA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

^e <https://www.cff.org/Care/Clinical-Care-Guidelines/>

The clinical development program for TEZ/IVA included two multicenter, randomized, double-blind, placebo-controlled Phase 3 trials of patients with CF 12 years of age and older who were either F508del homozygous or were F508del heterozygous with a second allele that results in residual CFTR function. A third Phase 3 study in CF patients who were heterozygous for the F508del mutation with a second CFTR mutation not responsive to TEZ/IVA was terminated early because the pre-specified futility criteria were met. The third study will not be discussed further in this review because the genotypes evaluated are not part of the proposed indication for TEZ/IVA.

- Study 106 (NCT02347657) evaluated 504 patients who are F508del homozygous that were randomized 1:1 to receive either placebo or TEZ/IVA for 24 weeks. The patients continued their normal, stable maintenance treatment for CF symptoms during the study. The primary efficacy endpoint was the absolute change in percent predicted FEV₁ (ppFEV₁) through Week 24. Patients who completed the Week 24 visit could enroll in an open-label extension study if eligible.
- Study 108 (NCT02392234) evaluated 478 patients who are F508del heterozygous with a mutation on the second CFTR allele that results in residual CFTR function. The patients were randomized to one of six different treatment arms using a 2-period, 3-treatment crossover design (TEZ/IVA; ivacaftor single-agent therapy; placebo) that included two 8-week treatment periods and a washout of at least 8 weeks between treatment periods. The study schematic is shown below in Figure 1. The patients continued their normal, stable maintenance treatment for CF symptoms during the study. The primary efficacy endpoint was the absolute change in ppFEV₁ from study baseline to the average of Week 4 and Week 8 measurements in each treatment period. Patients who completed the Week 24 visit could enroll in the open-label extension study if eligible.



Multiple key secondary endpoints were also evaluated in the studies, including the relative change in ppFEV₁ from study baseline, the absolute change in body mass index (BMI), the absolute change in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score,^f and CFTR function as measured by sweat chloride concentration, among other endpoints.

^f The CFQ-R is a validated health-related quality of life measure (HRQOL) containing generic and CF-specific scales that measures functioning during the previous 2 weeks. Each CFQ-R scale yields standardized scores ranging from 0 to 100, with higher scores indicating better HRQOL.

In Study 106, treatment with TEZ/IVA demonstrated statistically significant improvement in absolute change in ppFEV₁ compared to placebo. The least squares (LS) mean treatment difference for the absolute change from baseline in ppFEV₁ through Week 24 was 4.0 percentage points (p < 0.0001). The mean change from baseline in ppFEV₁ was 3.4 percentage points in the TEZ/IVA group versus -0.6 in the placebo group through Week 24. In terms of secondary endpoints, the LS mean treatment difference for the relative change from baseline in ppFEV₁ through Week 24 was 6.8 percent (p < 0.0001) in favor of TEZ/IVA. BMI increased in both the TEZ/IVA and placebo treatment groups at Week 24; although the LS mean absolute change from baseline in BMI was numerically greater in the TEZ/IVA group compared with the placebo group, the treatment difference of 0.06 mg/m² was not statistically significant (p = 0.4127). Treatment with TEZ/IVA also resulted in statistically or nominally significant improvements in the CFQ-R respiratory domain score and the sweat chloride concentration from baseline through Week 24.

In Study 108, the LS mean treatment difference for the TEZ/IVA group versus placebo for the absolute change from study baseline in ppFEV₁ to the average of Week 4 and Week 8 was 6.8 percentage points (p < 0.0001). The LS mean treatment difference for the IVA group versus placebo was 4.7 percentage points (p < 0.0001), and the LS mean treatment difference for the TEZ/IVA group versus IVA was 2.1 percentage points (p < 0.0001). Treatment with TEZ/IVA and IVA resulted in statistically significant improvements in the CFQ-R respiratory domain score from study baseline to the average of Week 4 and Week 8 compared with placebo; the treatment difference for the TEZ/IVA group versus IVA did not show a statistically significant difference. Treatment with TEZ/IVA resulted in statistically significant reductions from baseline in sweat chloride concentration compared with placebo as well as ivacaftor monotherapy.

The clinical reviewer concluded there are consistent findings of efficacy of TEZ/IVA in Studies 106 and 108 with respect to the absolute change in ppFEV₁, which is supported by secondary efficacy endpoints including the relative change in ppFEV₁, and the improvements in CFQ-R respiratory domain and sweat chloride concentration.⁶ In Study 108, the combination of TEZ/IVA compared with ivacaftor monotherapy showed a significant difference in ppFEV₁ from baseline in favor of the combination therapy. Although there was no ivacaftor monotherapy arm in Study 106, TEZ/IVA showed a 4.0% difference from placebo in the absolute change in ppFEV₁. This difference is similar to the treatment difference observed in ppFEV₁ between the FDA-approved combination of lumacaftor/ivacaftor and placebo at Week 24, which was 2.6 - 3.0%.^{g,5}

5 Risk Assessment & Safe-Use Conditions

In the pooled placebo-controlled Phase 3 studies, 505 patients received placebo, 496 patients received TEZ/IVA, and 157 patients received ivacaftor monotherapy.⁷

5.1 SERIOUS ADVERSE EVENTS^{h,i}

^g FDA factor (C): The expected benefit of the drug with respect to such disease or condition.

^h Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug

Although there were no deaths reported in the clinical trials, the Applicant's 120-Day Safety Update⁸ reported one death that occurred during the open label extension study. The patient experienced an infective pulmonary exacerbation and respiratory failure related to cystic fibrosis and acute influenza, which led to multisystem organ failure. The clinical reviewer did not find a causal link between the fatal outcome and TEZ/IVA.⁹

In the placebo-controlled Phase 3 studies, nonfatal serious adverse events (SAEs) were more frequently reported in the placebo group (14.9% [75/505]) compared with the TEZ/IVA group (10.1% [50/496]) or with the patients who received IVA monotherapy (6.4% [10/157]). Table 1 below lists the SAEs by MedDRA preferred term occurring in at least 2 patients in any group. The clinical reviewer noted two patients in the IVA group experienced increased blood CPK levels; otherwise, most SAEs were typical of events one might expect to occur in CF patients.

Table 1. Serious Adverse Events in the placebo controlled Phase 3 studies occurring in ≥2 patients in any group

System Organ Class	Preferred Term	Placebo [N=505] n (%)	TEZ/IVA [N=496] n (%)	IVA [N=157] n (%)
Infections	Infective pulmonary exacerbation of cystic fibrosis	52 (10.3)	33 (6.7)	6 (3.8)
Infections	Pneumonia	3 (0.6)	2 (0.4)	0
Infections	Influenza	2 (0.4)	1 (0.2)	0
Respiratory	Haemoptysis	6 (1.2)	5 (1.0)	1 (0.6)
Gastrointestinal	Distal intestinal obstruction syndrome	0	3 (0.6)	1 (0.6)
Gastrointestinal	Abdominal pain	2 (0.4)	0	0
Gastrointestinal	Constipation	2 (0.4)	0	0
Investigations	Pulmonary function test decreased	3 (0.6)	0	0
Investigations	Blood CPK increased	1 (0.2)	1 (0.2)	2 (1.3)
Renal	Acute kidney injury	2 (0.4)	0	0

5.2 SEVERE ADVERSE EVENTS

In the placebo-controlled Phase 3 studies, severe adverse events (Grade 3/4) were reported in 43 (8.5%) patients in the placebo group compared with 35 (7.1%) patients in the TEZ/IVA group and 8 (5.1%) patients who received ivacaftor monotherapy. There were no imbalances of note in the incidence of individual severe adverse events between the placebo group and treatment groups. The clinical reviewer noted the severe adverse events were primarily associated with CF disease-related events.⁶

experience when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

ⁱ FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

5.3 ADVERSE EVENTS OF SPECIAL INTEREST

5.3.1 Elevated Liver Function Tests

The percentage of patients in the placebo and TEZ/IVA Phase 3 study groups who experienced elevations in transaminases was low and similar between the placebo (3.6%) and TEZ/IVA (3.4%) groups. There were no elevated transaminase adverse events that were considered serious. Two patients experienced events leading to treatment discontinuation in the placebo group compared with one patient in the TEZ/IVA group. The incidences of transaminase elevations >8x, >5x, or >3x the upper limit of normal (ULN) were similar in the placebo and TEZ/IVA groups, as were elevations in total bilirubin >3x or >2x ULN. There was one Hy's law case that occurred in the placebo group. Table 2 below shows a threshold analysis of liver function tests in the placebo and TEZ/IVA groups.

Table 2. Threshold analysis of liver function tests in the placebo controlled Phase 3 studies

Liver function test (unit) Threshold analysis	Placebo [N=505] n/N1 (%)	TEZ/IVA [N=496] n (%)
ALT or AST (U/L)		
>3 to ≤5 x ULN	12/504 (2.4)	12/494 (2.4)
>5 to ≤8 x ULN	3/504 (0.6)	4/494 (0.8)
>8 to ≤20 x ULN	2/504 (0.4)	1/494 (0.2)
>20 x ULN	0/504	0/494
Total bilirubin (μmol/L)		
>1.5 to ≤2 x ULN	6/504 (1.2)	11/494 (2.2)
>2 to ≤3 x ULN	7/504 (1.4)	4/494 (0.8)
>3 to ≤10 x ULN	1/504 (0.2)	2/494 (0.4)
>10 x ULN	0/504	0/494

N1 is the number of patients with at least one non-missing measurements during the treatment-emergent period; n is the number of patients who met the threshold analysis criteria.

5.3.2 Cataracts

The incidence of cataracts in patients at baseline varied by study: 5.1% of patients in Study 106 and 11.4% of patients in Study 108. Adverse event data were not pooled in the placebo-controlled Phase 3 studies because only Study 106 was long enough (24-week treatment duration) to allow detection of treatment-emergent cataracts. In Study 106, the incidence of treatment-emergent cataracts in the placebo group (5.2% [11/212]) was similar to that in the TEZ/IVA group (6.9% [14/203]). The clinical review noted that cataracts are a known safety signal observed with ivacaftor monotherapy and with the related CFTR modulator product lumacaftor/ivacaftor.

6 Expected Postmarket Use

The most likely prescribers of TEZ/IVA are experts in the care of CF and will include pulmonologists and other specialists who are part of the multidisciplinary clinical teams who manage patients with CF. As an

orally administered drug, TEZ/IVA will likely primarily be administered by patients or caregivers in the outpatient setting as a chronic therapy.

7 Risk Management Activities Proposed by the Applicant

The Applicant submitted a risk management plan that proposes routine pharmacovigilance and use of the product labeling.

8 Discussion of Need for a REMS

Cystic fibrosis is a serious, progressive, multisystem, life-shortening, genetic disease of children and adults that results from a defective CFTR chloride channel on epithelial cells. Based on the observed improvements in ppFEV₁, CFQ-R, and the sweat chloride concentration in the Phase 3 trials, TEZ/IVA is efficacious for the treatment of patients who are either F508del homozygous or with at least one CFTR mutation responsive to TEZ/IVA based on in vitro data and/or clinical evidence. The combination of TEZ/IVA compared with ivacaftor monotherapy showed a significant improvement in ppFEV₁ from baseline in favor of TEZ/IVA. TEZ/IVA also showed an improvement in ppFEV₁ that is comparable to the treatment difference observed for the FDA-approved combination of lumacaftor/ ivacaftor (Orkambi) albeit for patients with a different genetic profile.

The most important safety concerns associated with TEZ/IVA include elevated liver function tests and cataracts. There was a similar incidence of elevated LFTs in the TEZ/IVA and placebo groups, and none of the elevations associated with TEZ/IVA met the criteria for Hy's law. There was also a similar incidence of cataracts in the TEZ/IVA group compared with the placebo group. The ivacaftor label lists transaminase elevations and cataracts under the warnings and precautions section, which includes recommendations for monitoring. The Applicant has proposed similar warnings and precautions for elevated liver function tests and cataracts in the TEZ/IVA label. There is an absence of new safety concerns unique to the TEZ/IVA combination compared with the use of ivacaftor as a single-agent treatment for CF. Additionally, the safety profile for TEZ/IVA is similar to that of Orkambi, which has labeling that includes warnings and precautions for liver-related events, respiratory events, effects on blood pressure, and cataracts. The approval of Orkambi did not require a REMS.

Based on the observed benefit of TEZ/IVA, the serious, progressive, and life-shortening nature of the disease, and the expectation that TEZ/IVA will only be prescribed by physicians with expertise in the management and monitoring of patients with CF, DRISK is not recommending a REMS for the management of the potential risks of TEZ/IVA.

9 Conclusion & Recommendations

Based on the currently available data, there is an absence of new safety concerns unique to the TEZ/IVA combination compared with the use of ivacaftor as a single-agent treatment for CF. The most important safety concerns for TEZ/IVA are comparable to those for ivacaftor, which does not require a REMS.

Therefore, DRISK recommends that a REMS is not necessary to ensure the benefits of TEZ/IVA outweigh the risks.

Should DPARP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 REFERENCES

- ¹ Katkin JP. Cystic fibrosis: Genetics and pathogenesis. In:UpToDate, Mallory GB, Hoppin AG (Eds), UpToDate, Waltham, MA 2017.
- ² Katkin JP. Cystic fibrosis: Clinical manifestations and diagnosis. In:UpToDate, Mallory GB, Hoppin AG (Eds), UpToDate, Waltham, MA 2017.
- ³ Cystic Fibrosis Foundation Patient Registry. 2016 Annual Data Report. Bethesda, MD, 2017.
- ⁴ Simon RH. Cystic fibrosis: Overview of the treatment of lung disease. In:UpToDate, Mallory GB, Hoppin AG (Eds), UpToDate, Waltham, MA 2017.
- ⁵ Orkambi®(lumacaftor and ivacaftor) product labeling. Vertex Pharmaceuticals, Inc., Boston, MA; September 2016.
- ⁶ Chin S. Division of Pulmonary, Allergy, and Rheumatology Products. Midcycle Meeting Clinical Slides, NDA 210491, October 19, 2017.
- ⁷ Vertex Pharmaceuticals. Summary of Clinical Safety for tezacaftor/ivacaftor, NDA 210491, June 28, 2017.
- ⁸ Vertex Pharmaceuticals. 120-Day Safety Update for tezacaftor/ivacaftor, NDA 210491, September 21, 2017.
- ⁹ Chin S. Division of Pulmonary, Allergy, and Rheumatology Products. Clinical Review, NDA 210491, February 1, 2018.

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/s/

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02/05/2018

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