CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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	212273
PDUFA Goal Date	March 19, 2020
OSE RCM #	2019-1547
Reviewer Name(s)	Bob Pratt, Pharm.D.
Team Leader	Donella Fitzgerald, Pharm.D.
Deputy Division Director	Jamie Wilkins, Pharm.D.
Review Completion Date	October 16, 2019
Subject	Evaluation of need for a REMS
Established Name	Elexacaftor/Tezacaftor/Ivacaftor
Trade Name	Trikafta™
Name of Applicant	Vertex Pharmaceuticals Inc.
Therapeutic Class	CFTR corrector/potentiator
Formulation(s)	Elexacaftor/Tezacaftor/Ivacaftor 100 mg/50 mg/75 mg oral tablet and Ivacaftor 150 mg oral tablet
Dosing Regimen	Elexacaftor/Tezacaftor/Ivacaftor 100/50/75: 2 tablets in the morning Ivacaftor 150: 1 tablet in the evening (Elexacaftor 200 mg once daily/Tezacaftor 100 mg once daily/Ivacaftor 150 mg twice daily)

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Trikafta™ (elexacaftor/tezacaftor/ivacaftor) is necessary to ensure the benefits of this product outweigh the risks. Vertex Pharmaceuticals submitted a New Drug Application (NDA 212273) on July 19, 2019, with the proposed indication for the treatment of patients with cystic fibrosis (CF) age 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Elexacaftor is the new molecular entity (NME) component of the drug combination. Ivacaftor is approved for the treatment of cystic fibrosis in patients who have one mutation in the CFTR gene that is responsive to ivacaftor potentiation of chloride transport. Ivacaftor is also approved for use in combination with the CFTR corrector lumacaftor for patients who are homozygous for the F508del mutation, and for use in combination with the CFTR corrector tezacaftor for patients who are homozygous for the F508del mutation or heterozygous for F508del with a residual function CFTR mutation on the second allele. The most important safety concerns associated with elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) are elevated liver transaminases and cataracts. The Applicant submitted a risk management plan that proposes routine pharmacovigilance and the 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. ELX/TEZ/IVA showed substantial evidence of efficacy in the treatment of CF in patients 12 years of age and older who have at least one F508del mutation in the CFTR gene. The Division of Risk Management (DRISK) has determined that a REMS is not needed to ensure the benefits of ELX/TEZ/IVA outweigh its risks. Based on the currently available data, there is an absence of new safety concerns unique to the ELX/TEZ/IVA combination compared with ivacaftor when used as either a single-agent treatment or in combination with lumacaftor or tezacaftor.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Trikafta™ (elexacaftor/tezacaftor/ivacaftor) is necessary to ensure the benefits of this product outweigh its risks. Vertex Pharmaceuticals (Vertex) submitted a New Drug Application (NDA 212273) on July 19, 2019, with the proposed indication for the treatment of patients with cystic fibrosis (CF) age 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. 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 the use of the product labeling.

2 Background

2.1 PRODUCT INFORMATION

Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) is a fixed dose combination of two CFTR correctors and one CFTR potentiator with the proposed indication for the treatment of patients with cystic fibrosis 12 years of age and older who have at least one copy of an F508del mutation in the CFTR gene. 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 functionality. Elexacaftor (ELX), the NME component of the drug combination[a], and tezacaftor (TEZ) are CFTR correctors that act on the defective gene product to improve its cellular processing and trafficking and thus increase the amount of CFTR at the cell surface. The two correctors bind at different sites on the CFTR protein and have an additive effect.[1] Ivacaftor (IVA) facilitates increased chloride transport by potentiating the channel open probability (or gating) of CFTR at the cell surface. Therefore, the combination of ELX/TEZ/IVA intends to increase the quantity and gating function of CFTR at the cell surface, resulting in increased chloride ion transport in patients who have at least one copy of an F508del mutation.

Trikafta™ is a chronic therapy[b] supplied as an ELX/TEZ/IVA fixed dose combination tablet containing 100 mg, 50 mg, and 75 mg of each drug, respectively, and a separate ivacaftor 150 mg tablet. The proposed dosing, which will be packaged in a weekly blister card, is two ELX/TEZ/IVA tablets in the morning and a single tablet containing 150 mg of IVA taken in the evening. ELX/TEZ/IVA received Breakthrough Therapy designation on May 15, 2018, and orphan product designation on August 29, 2018. ELX and ELX/TEZ/IVA are not currently approved in any other jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 212273 relevant to this review:

- 5/15/2018: Breakthrough Therapy designation granted for the treatment of cystic fibrosis in patients homozygous for the F508del mutation or who have an F508del mutation on one allele and a second allele with a minimal CFTR function mutation.
- 8/29/2018: Orphan product designation granted for the treatment of cystic fibrosis.
- 7/19/2019: NDA 212273 submission for the treatment of cystic fibrosis.
- 9/19/2019: A post mid-cycle meeting was held between the Agency and the Applicant via teleconference. There was no discussion related to a REMS or risk management.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Cystic fibrosis is an autosomal recessive disease resulting in a defective CFTR protein, which causes aberrant transport of chloride and water across epithelial cells in multiple organs. CF affects at least 30,000 individuals in the U.S.[c,2] Over 2,000 mutations in the CFTR gene have been identified, with the most common mutation identified as F508del; at least one copy of this mutation is found in approximately 90% of CF patients, and 50% of CF patients are homozygous for the mutation.[3] Deranged transport of chloride and other CFTR-affected ions, such as sodium and bicarbonate, leads to thick, viscous secretions in the lungs, pancreas, liver, intestine, and reproductive tract, and patients with CF can develop multisystem disease involving several or all of these organs. Typical pulmonary manifestations include chronic airway

[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.
[c] FDAAA factor (A): The estimated size of the population likely to use the drug involved.

obstruction caused by viscous respiratory secretions, chronic pulmonary infection, and chronic inflammation. These conditions ultimately advance 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 manifestations.[4] Obstructive lung disease is the primary cause of morbidity and mortality. The median age at death was 30.6 years for the 380 people reported to have died in 2017 in the Cystic Fibrosis Foundation Registry. Over the 5-year period of 2013 to 2017, the predicted median survival of individuals born during that period is 43.6 years.[2,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; 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.

Molecular Therapy

Current molecular therapy for cystic fibrosis includes the CFTR potentiator IVA and the CFTR correctors lumacaftor and TEZ. IVA is approved for single-agent use and in combination with lumacaftor or TEZ. Lumacaftor and TEZ act by correcting processing and trafficking of the CFTR protein, whereas IVA improves the gating abnormality of the defective protein. The indications and efficacy of these treatments depend on the CFTR mutations found in the individual patient. Table 1 below shows the indications and safety profiles of the currently approved molecular therapy for CF.

IVA (Kalydeco®) 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 led to an expansion of the list of CFTR mutations responsive to IVA such that the product label currently shows 38 mutations as being responsive.[5,6]

For individuals who are homozygous for the F508del mutation, treatment with the combination of IVA and lumacaftor (Orkambi®) is indicated for CF patients who are two years of age and older.[7] However, lumacaftor is a strong inducer of CYP3A and IVA is a CYP3A substrate, resulting in a drug-drug interaction that reduces IVA exposure and limits clinical efficacy. (Other strong inducers of CYP3A, such as rifampin, also substantially decrease exposure of ivacaftor.) The combination of IVA and TEZ (Symdeko®) is indicated for the treatment of patients who are 6 years of age and older and homozygous for the F508del mutation or heterozygous for F508del with a residual function CFTR mutation on the second allele.[8]

Even though most CF patients have at least one copy of an F508del mutation, none of the currently-approved therapies have a large enough effect on F508del-CFTR to support an indication for treating patients who are heterozygous F508del with a *minimal* function CFTR gene mutation. The proposed combination of two CFTR correctors (ELX and TEZ) with distinct binding sites increases the amount of CFTR

[d] FDAAA 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

at the cell surface more so than with either corrector alone. Because of the additive effect on CFTR, the use of ELX and TEZ in combination with IVA is proposed for the treatment of patients who are heterozygous F508del without regard to the mutation on the second gene.

Table 1: Molecular therapies approved in the U.S. for cystic fibrosis

Product Name (Trade Name) Year of Approval	Indication	Warnings and Precautions
Ivacaftor (Kalydeco) 2012	Treatment of cystic fibrosis in patients age 6 months 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.	• Transaminase elevations • Concomitant use with CYP3A inducers • Cataracts
Ivacaftor/Lumacaftor (Orkambi) 2015	Treatment of cystic fibrosis in patients age 2 years and older who are homozygous for the F508del mutation in the CFTR gene.	• Use in advanced liver disease • Liver-related events • Respiratory events • Blood pressure effects • Drug interactions • Cataracts
Ivacaftor/Tezacaftor (Symdeko) 2018	Treatment of patients with cystic fibrosis age 6 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 tezacaftor/ivacaftor based on in vitro data and/or clinical evidence.	• Transaminase elevations • Concomitant use with CYP3A inducers • Cataracts

4 Benefit Assessment

The clinical development program for ELX/TEZ/IVA includes two multicenter, randomized, double-blind, placebo- or active-controlled, parallel-group Phase 3 trials of patients with CF 12 years of age and older.

- Study 102 (NCT03525444) evaluated 403 patients who are heterozygous for F508del with a minimal function mutation on the second allele. Patients were randomized 1:1 to receive either placebo or ELX/TEZ/IVA for up to 24 weeks. The patients could remain on a stable background of standard-of-care therapy for CF during the study. The primary efficacy endpoint was the absolute change in percent predicted FEV_1 ($ppFEV_1$) from baseline at Week 4. A 24-week treatment duration was selected to allow for the collection of placebo-controlled safety data as well as the collection of data for secondary outcomes that require longer treatment durations to demonstrate an effect. Patients who completed the study could enroll in an open-label extension study for up to 96 weeks if eligible.

- Study 103 (NCT03525548) evaluated 107 patients who are F508del homozygous. Following a 4-week run-in period on TEZ/IVA, patients were randomized 1:1 to receive either ELX/TEZ/IVA or TEZ/IVA for 4 weeks. The patients could remain on a stable background of standard-of-care therapy for CF during the study. The primary efficacy endpoint was the absolute change in $ppFEV_1$ from baseline at Week 4. Study 103 had a 4-week treatment duration because previous studies of TEZ/IVA had demonstrated that

efficacy related to lung function can be reliably established at Week 4. Patients who completed the study could enroll in an open-label extension study for up to 96 weeks if eligible.

Multiple key secondary endpoints were also evaluated in the studies, including the absolute change from baseline in ppFEV$_1$ through Week 24, the rate of pulmonary exacerbations through Week 24, the absolute change from baseline in sweat chloride, the absolute change in the Cystic Fibrosis Questionnaire-Revised respiratory domain (CFQ-R RD) score,[f] and the absolute change in body mass index (BMI) at Week 24, among other endpoints.

In Study 102, treatment with ELX/TEZ/IVA demonstrated a statistically significant improvement in the absolute change in ppFEV$_1$ compared to placebo. The least squares (LS) mean treatment difference at Week 4 was 13.8 percentage points (95% CI: 12.1, 15.4; p<0.0001) higher in the ELX/TEZ/IVA group than in the placebo group. For the key secondary endpoints, the LS mean treatment difference in ppFEV$_1$ at Week 24 was 14.3 percentage points (95% CI: 12.7, 15.8; p<0.0001) higher in the ELX/TEZ/IVA group compared with the placebo group. Week 24 comparisons between the ELX/TEZ/IVA group and the placebo group showed a significant reduction in the rate of pulmonary exacerbations, and significant improvements in the sweat chloride concentration, CFQ-R RD scores, and BMI in the ELX/TEZ/IVA group compared with the placebo group.

In Study 103, treatment with ELX/TEZ/IVA demonstrated a statistically significant improvement in absolute change in ppFEV1 compared to TEZ/IVA. The least squares (LS) mean treatment difference at Week 4 was 10.0 percentage points (95% CI: 7.4, 12.6; p<0.0001) higher in the ELX/TEZ/IVA group than in the TEZ/IVA group. For the key secondary endpoints, there were significant improvements at Week 4 in the sweat chloride concentration and the CFQ-R RD scores in the ELX/TEZ/IVA group compared with the TEZ/IVA group.

The clinical reviewer concluded there are consistent findings of efficacy of ELX/TEZ/IVA in Studies 102 and 103. ELX/TEZ/IVA demonstrated a robust lung function benefit with respect to the absolute change in ppFEV$_1$, which is supported by clinically meaningful secondary efficacy endpoint results that showed significant improvements in pulmonary exacerbation rate, CFQ-R RD respiratory domain score, sweat chloride concentration, and BMI.[g]

5 Risk Assessment & Safe-Use Conditions

In the clinical development program, a total of 619 unique patients were exposed to ELX/TEZ/IVA in the controlled Phase 3 studies, open-label extension study, Phase 2 study, and an open-label study in patients who were 6 through 11 years of age. The Phase 3 program included a combined 257 patients exposed to ELX/TEZ/IVA.

[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. The respiratory domain score is a measure of respiratory symptoms such as cough, sputum production, and difficulty breathing.

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

5.1 SERIOUS ADVERSE EVENTS [h,i]

There were no deaths reported in the clinical development program or in the open-label extension.[9,10]

In Study 102, 28 (14%) patients in the ELX/TEZ/IVA group and 42 (21%) patients in the placebo group had at least one serious adverse event (SAE). The most frequently reported SAE in each group was infective pulmonary exacerbation of cystic fibrosis, which occurred in 11 patients in the treatment group and 33 patients in the placebo group. Other SAEs reported at least two times in the ELX/TEZ/IVA group included influenza (n=3), rash (n=3), hemoptysis (n=2), and intestinal obstruction (n=2).

In Study 103, 2 (4%) patients in the ELX/TEZ/IVA group had SAEs, which included infective pulmonary exacerbation of cystic fibrosis, and rash. In the comparator TEZ/IVA group, one (2%) patient had an SAE of infective pulmonary exacerbation of cystic fibrosis.

There was one SAE of rhabdomyolysis and increased blood creatine phosphokinase (CPK) levels reported in a patient in the ELX/TEZ/IVA group of Study 102, though the clinical reviewer thought the case did not likely meet criteria for clinical rhabdomyolysis. Otherwise, the SAEs observed in the two studies were typical of events seen in CF patients.

5.2 SEVERE ADVERSE EVENTS

In Study 102, severe (but non-life-threatening) adverse events were reported in 18 (9%) patients in the ELX/TEZ/IVA group compared with 14 (7%) patients in the placebo group. Severe events that were reported at least two times in the ELX/TEZ/IVA group included blood CPK increased (n=4), aspartate aminotransferase (AST) increased (n=2), alanine aminotransferase (ALT) increased (n=2), and abdominal pain (n=2), whereas severe events in the placebo group included infective pulmonary exacerbation of cystic fibrosis (n=9). One patient in the placebo group experienced a life-threatening adverse event.

In Study 103, one patient in the TEZ/IVA group had a severe AE of musculoskeletal pain. There were no severe (or life-threatening) adverse events reported in the ELX/TEZ/IVA group.

5.3 ADVERSE EVENTS OF SPECIAL INTEREST

5.3.1 Elevated Liver Function Tests

The percentage of patients in Study 102 who experienced elevations in liver function tests (LFTs) was greater in the ELX/TEZ/IVA group compared with the placebo group. There were no elevated transaminase adverse events in the treatment group considered to be serious. The percentages of transaminase elevations >8x, >5x, or >3x the upper limit of normal (ULN) were greater in the ELX/TEZ/IVA group compared with the placebo group, as were elevations in total bilirubin >1.5x, >2x, and >3x to ≤10x ULN. There were two

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[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 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.

patients in the treatment group whose LFTs met the biochemical criteria for Hy's law. In one case, the elevation in bilirubin occurred at the time transaminase levels were decreasing to near baseline. The second case happened in a patient with Gilbert's syndrome who had an elevated bilirubin level at baseline. The clinical review team did not have concerns that either of these cases represented drug-induced liver injury.

Table 2 below shows a threshold analysis of liver function tests in the Study 102 groups.

Table 2. Post-baseline threshold analysis of liver function tests in Study 102

Liver function test (unit)	Placebo [N=201] n (%)	ELX/TEZ/IVA [N=202] n (%)
ALT or AST (U/L)		
>3 to ≤5 x ULN	11 (5.5%)	16 (7.9%)
>5 to ≤8 x ULN	3 (1.5%)	5 (2.5%)
>8 to ≤20 x ULN	2 (1.0%)	3 (1.5%)
Total bilirubin (µmol/L)		
>1.5 to ≤2 x ULN	2 (1.0%)	12 (5.9%)
>2 to ≤3 x ULN	1 (0.5%)	7 (3.5%)
>3 to ≤10 x ULN	0	1 (0.5%)

N=the number of patients with at least one non-missing measurement during the treatment-emergent period
n=the number of patients in the post-baseline category; Source: Study 102 Clinical Study Report Table 14.3.4.2.

In Study 103, two (3.6%) patients in the ELX/TEZ/IVA group and one (1.9%) patient in the TEZ/IVA group had at least one elevated transaminase event. The adverse events were non-serious and mild in severity.

5.3.2 Cataracts

Cataracts are a known safety signal observed with ivacaftor monotherapy. In Study 102, baseline and follow-up ophthalmologic examinations were performed. One patient in the ELX/TEZ/IVA group experienced a non-serious adverse event of cataract and lenticular opacity. The patient had a history of CF-related diabetes and concomitant use of corticosteroids. In the placebo group, one patient developed mild cataracts on Study Day 7. There were no adverse events of cataract in Study 103.

6 Expected Postmarket Use

The most likely prescribers of ELX/TEZ/IVA are experts in the care of CF and would include pulmonologists and other specialists who are part of the multidisciplinary clinical teams who manage patients with CF. As an orally administered drug, ELX/TEZ/IVA will likely be primarily 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

The clinical reviewer concluded that substantial evidence of clinical efficacy has been established for the use of ELX/TEZ/IVA in CF patients who have at least one F508del mutation.

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. The placebo-controlled Phase 3 studies demonstrate a robust lung function benefit with respect to the absolute change in $ppFEV_1$, which is supported by clinically meaningful secondary endpoints that include improvements in pulmonary exacerbation rate, CFQ-R RD respiratory domain score, sweat chloride concentration, and BMI. ELX/TEZ/IVA is efficacious for the treatment of patients who have at least one F508del mutation. In patients who are homozygous F508del, ELX/TEZ/IVA showed significant improvements in $ppFEV_1$ as well as in secondary endpoints compared with TEZ/IVA.

The most important risks associated with ELX/TEZ/IVA include elevated LFTs and cataracts. The percentage of patients in Study 102 with LFT elevations was greater in the ELX/TEZ/IVA group compared with the placebo group for all post-baseline categories. However, no cases associated with ELX/TEZ/IVA were assessed as drug-induced liver injury by the clinical review team. The proposed labeling includes a warning and precaution for LFT elevations along with recommendations for monitoring. Cataracts are a known risk associated with ivacaftor therapy, and the product labels for ivacaftor and the ivacaftor-containing regimens of Orkambi and Symdeko include a warning and precaution for cataracts as well as recommendations for ophthalmological monitoring; the proposed label for ELX/TEZ/IVA includes a similar warning and precaution. Rash and elevated CPK levels are additional safety concerns identified in the ELX/TEZ/IVA studies that will be described in the adverse reactions section of the label.

There is an absence of new safety concerns unique to the ELX/TEZ/IVA combination compared with the use of TEZ/IVA therapy for the treatment of CF. Additionally, the safety profile for ELX/TEZ/IVA is similar to that of Orkambi, which has labeling that includes warnings and precautions for liver-related events and cataracts, among other warnings. The approvals of TEZ/IVA and Orkambi did not require a REMS.

Based on the observed benefit of ELX/TEZ/IVA, the serious, progressive, and life-shortening nature of the disease, and the expectation that ELX/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 ELX/TEZ/IVA.

9 Conclusion & Recommendations

Based on the currently available data, there is an absence of new safety concerns unique to the ELX/TEZ/IVA combination compared with the use of TEZ/IVA therapy for CF. The most important safety concerns for ELX/TEZ/IVA are similar to the other treatment combinations in the class, none of which required a REMS. Therefore, DRISK recommends that a REMS is not necessary to ensure the benefits of ELX/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] Draft Multi-disciplinary Review, NDA 212273, September 20, 2019.

[2] Cystic Fibrosis Foundation Patient Registry, 2017 Annual Data Report, Bethesda, Maryland.

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[5] Kalydeco® (ivacaftor) product labeling. Vertex Pharmaceuticals, Inc., Boston, MA.

[6] Simon RH. Cystic fibrosis: Overview of the treatment of lung disease. In:UpToDate, Mallory GB, Hoppin AG (Eds), UpToDate, Waltham, MA 2017.

[7] Orkambi®(lumacaftor and ivacaftor) product labeling. Vertex Pharmaceuticals, Inc., Boston, MA.

[8] Symdeko®(tezacaftor and ivacaftor) product labeling. Vertex Pharmaceuticals, Inc., Boston, MA.

[9] Vertex Pharmaceuticals. Summary of Clinical Safety for elexacaftor/tezacaftor/ivacaftor, NDA 212273, July 19, 2019.

[10] Vertex Pharmaceuticals. Safety Update for elexacaftor/tezacaftor/ivacaftor, NDA 212273, August 30, 2019.

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