CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218730Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
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	218730
PDUFA Goal Date	January 2, 2025
Nexus TTT #	2024-9426
Reviewer Name(s)	May L Chan-Liston, PharmD, MPH
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	December 18, 2024
Subject	Evaluation of Need for a REMS
Established Name	Vanzacaftor/Tezacaftor/Deutivacaftor Triple Combination Therapy
Trade Name	Alyftrek
Name of Applicant	Vertex Pharmaceuticals, Inc.
Therapeutic Class	CF transmembrane conductance regulator protein (*CFTR*) modulator
Formulation(s)	Tablets
Dosing Regimen	

Recommended Dosage for people with CF aged 6 years and older		
Age	**Weight**	**Daily Dose (once daily)**
		(b) (4)

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Alyftrek (vanzacaftor, tezacaftor, and deutivacaftor) is necessary to ensure the benefits outweigh its risks. Vertex Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 218730 for the fixed combination of vanzacaftor, tezacaftor, and deutivacaftor (VNZ/TEZ/D-IVA) with the proposed indication for the treatment of cystic fibrosis (CF) in people with CF aged 6 years and older who have at least one *F508del* mutation or another responsive mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. This application is under review in the Division of Pulmonology, Allergy, and Critical Care.[1] The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Vanzacaftor, tezacaftor, and deutivacaftor (VNZ/TEZ/D-IVA), a new molecular entity, is a regimen composed of 3 *CFTR* modulators proposed for the treatment of cystic fibrosis (CF) in people with CF aged 6 years and older who have at least one *F508del* mutation or another responsive mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Alyftrek is proposed as fixed-dosed combination tablets with two strength options: 1.) vanzacaftor 4 mg, tezacaftor 20 mg, and deutivacaftor 50 mg and 2.) vanzacaftor 10 mg, tezacaftor 50 mg, and deutivacaftor 125 mg. Dosage recommendations are weight dependent and should be given once a day with fat containing food. The combination of VNZ/TEZ/D-IVA is not currently approved in the United States or in any jurisdiction.[2]

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 218730 relevant to this review:

- 05/02/2024: NDA 218730 submission for the treatment of cystic fibrosis (CF) in people with CF aged 6 years and older who have at least one *F508del* mutation or another responsive mutation in the *CFTR* gene. The application is designated as Priority with an 8-month review time. The PDUFA is January 2, 2025.[2,3]
- 09/04/2024: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, no major safety concerns had been identified to date.

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 32,000 individuals in the U.S.[4] 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.[5] 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 obstruction caused by viscous respiratory secretions, chronic pulmonary infection, and chronic inflammation. These conditions 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.[6] In the Cystic Fibrosis Foundation Patient Registry, respiratory/cardiorespiratory causes were reported as the primary cause of death. The median age at death was 33.9 years for the 232 people reported in the registry that died in 2021.[7]

3.2. Description of Current Treatment Options

Although no cure exists, there are currently four approved CF therapies affecting *CFTR* processing or function. However, there is an unmet need for therapies for CF patients who are not currently eligible for or are intolerant of an approved therapy that affects CFTR function or processing. There remains an additional need in patients with persistent symptom burden despite therapy with an approved medication.[4] The approved products are below[4,8]:

Product Name (Trade Name) Year of Approval	**Indication**	**Warnings and Precautions**
Ivacaftor (Kalydeco) 2012	Treatment of cystic fibrosis 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	• Transaminase elevations • Concomitant use with CYP3A inducers • Cataracts

	responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence.	
Elexacaftor/Tezacaftor/Ivacaftor (Trikafta) 2019	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.	• Elevated transaminases and hepatic injury • Hypersensitivity reactions: Angioedema and anaphylaxis • Concomitant use with CYP3A inducers • Cataracts

4. Benefit Assessment

The Applicant submitted data from two phase 3 clinical trials, Trials 102 and 103, as the primary support for the safety and efficacy of VNZ/TEZ/D-IVA in CF subjects 12 years of age and older. These trials were both international, multicenter, randomized, double-blind, Elexacaftor/Tezacaftor/Ivacaftor (ELX/TEZ/IVA)-controlled noninferiority trials evaluating the efficacy and safety of VNZ/TEZ/D-IVA over 52 weeks.

Trial VX20-121-102 (Trial 102) included a 4-week run-in period during which all subjects received ELX/TEZ/IVA to establish a reliable on-treatment (ELX/TEZ/IVA) baseline for the treatment period. Subjects were then randomized 1:1 to receive VNZ/TEZ/D-IVA or ELX/TEZ/IVA for a 52-week treatment period. Randomization was stratified by: age at screening, $ppFEV_1$ during the run-in period (Day -14 clinic assessment), sweat chloride (SwCl) during the run-in period (Day -14 clinic assessment), and prior use of ELX/TEZ/IVA or medications that contain one or more of its components. A total of 435 subjects were enrolled in Trial 102 who were heterozygous for *F508del* and minimal function (MF) variant. The primary endpoint was absolute change from baseline in $ppFEV_1$ through Week 24. The key secondary endpoints were absolute change from baseline in SwCl through Week 24, proportion of subjects with SwCl <60 mmol/L through Week 24, and proportion of subjects with SwCl <30 mmol/L through Week 24. The clinical review team indicated that the primary endpoint of absolute change from baseline (CFB) in ppFEV1 through Week 24 demonstrated that VNZ/TEZ/D-IVA was noninferior to ELX/TEZ/IVA in $ppFEV_1$ and the results were supportive of the treatment effect of VNZ/TEZ/D-IVA. See the below table for results.

Table. Change From Baseline in $ppFEV_1$ Through Week 24 (FAS), Trial 102[4]

Endpoint/Parameter	ELX/TEZ/IVA (N=202)	VNZ/TEZ/D-IVA (N=196)
Absolute CFB[a] in $ppFEV_1$ through Week 24[b]		
n	193	187
LS mean (SE)	0.3 (0.3)	0.5 (0.3)
95% CI of LS mean	-0.3, 0.9	-0.1, 1.1
LS mean difference (95% CI)		0.2 (-0.7, 1.1)
1-sided p-value for noninferiority vs ELX/TEZ/IVA		<0.00001

Source: Statistical analyst. Software: R. adsl and adsp datasets.
[a] Baseline $ppFEV_1$ measured at Day 1. If predose Day 1 was missing, the most recent predose, nonmissing value on or after Day -14 visit was used.
[b] $ppFEV_1$ through Week 24 (estimated by averaging Weeks 16 and 24)
Abbreviations: CFB, change from baseline; CI, confidence interval; D-IVA, deutivacaftor; ELX, elexacaftor; FAS, full analysis set; IVA, ivacaftor; LS, least squares; N, number of subjects in treatment group; n, number of subjects included in analysis; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; SD, standard deviation, SE, standard error; TEZ, tezacaftor; VNZ, vanzacaftor; vs, versus

For the key secondary endpoint, there was a statistically significant decrease from baseline in SwCl through Week 24 for VNZ/TEZ/D-IVA compared to ELX/TEZ/IVA with a mean difference (95% CI) of -8.4 (-10.5, -6.3) mmol/L (p-value<0.0001). The clinical reviewer also inserts that since SwCl is a pharmacodynamic marker and not a predictive marker of disease response to treatment, the clinical implications of a treatment difference of approximately 8 mmol/L in change from baseline are unclear.

Trial 103 had the same overall design and endpoints as Trial 102. The majority of subjects in Trial 103 completed treatment (532, 92.8%) and the trial (543, 94.8%). Through Week 24, treatment with VNZ/TEZ/D-IVA (n=284) was also noninferior to ELX/TEZ/IVA (n=289) in the absolute change from baseline in $ppFEV_1$, which was the primary efficacy endpoint. The least squares (LS) mean difference was 0.2% (95% CI: -0.5%, 0.9%) in the full analysis set (FAS) population.

In addition, the Applicant submitted an interim analysis from Trial 105 to support the use of VNZ/TEZ/D-IVA in pediatric CF patients ages 6 to 11. Trial 105 is an ongoing two-part, multicenter, multicohort, open-label, pediatric, pharmacokinetic (PK) and safety study trial of VNZ/TEZ/D-IVA in pediatric CF subjects. The PK data for VNZ/TEZ/D-IVA administration in trial 105 demonstrated that systemic exposures were comparable to those observed in the adolescent and adult population. As with other similar medications in this population, the efficacy and safety in the 6- to 11-year-old CF population are usually extrapolated from the adolescent and adult population and applied to the 6- to 11-year-old CF population because of comparable systemic exposures and a common understanding that the disease process and expected response to treatment are largely the same across age groups.

5. Risk Assessment & Safe-Use Conditions

All clinical studies conducted as part of the VNZ/TEZ/D-IVA development program were evaluated for safety but the FDA review team focused on the Phase 3 development program, Trials 102 and 103.[4]

Both Phase 3 trials included a 4-week ELX/TEZ/IVA run-in period followed by a 52-week treatment period as discussed in Section 4. Given similarities between the trial designs and populations, the safety data from Trials 102 and 103 were pooled for analysis.

There were no reported deaths attributable to adverse events during the treatment period in the pooled Phase 3 safety database and many of the most common AEs reported are consistent with both the known safety profile of ELX/TEZ/IVA and the Phase 3 development for program ELX/TEZ/IVA. In addition, the reported AEs were consistent with expected event rates in the CF population. The rates of Serious Adverse Events (SAEs) in Trials 102 and 103 were generally balanced between trials. The small imbalance in SAEs between the pooled treatment arms is unlikely to be of clinical significance.

Pediatric safety (6-11 years) was also evaluated from the open-label Trial 105. Overall, the review team concluded the majority of AEs were mild to moderate and any SAEs reported were consistent with what would be expected in a pediatric CF population.

5.1. Adverse Events of Special Interest

Drug Induced Liver Injury (DILI) and Liver Failure

There were no cases of liver failure leading to death or liver transplant in the Phase 3 pooled safety database for VNZ/TEZ/D-IVA. There were five cases of non jaundiced DILI that were assessed as 'probably' or 'possibly' related to VNZ/TEZ/D-IVA. No subjects exposed to VNZ/TEZ/D-IVA had transaminase elevations with concurrent elevations in total bilirubin.

Transaminase elevations are a well described adverse reaction related to all approved medications that affect *CFTR* processing or function and have been historically included as a Warning and Precaution in the USPI of the approved products. During this review, a Safety Labeling Change was issued to ELX/TEZ/IVA to elevate the risk of drug-induced liver injury and liver failure from a Warning and Precaution to a Boxed Warning.

The overall assessment of the data was that, although there were no cases of concurrent transaminitis and bilirubin elevation in the VNZ/TEZ/D-IVA group, the available data supports that there is a risk of hepatocellular injury associated with VNZ/TEZ/D-IVA. Therefore, the Boxed Warning will be required for VNZ/TEZ/D-IVA as it is for ELX/TEZ/IVA.

Creatine Kinase Elevations

Overall, there were similar rates of creatine phosphokinase AEs between treatment arms; however, there was a small numerical increase in the overall number of increased blood creatinine phosphokinase AEs reported (VNZ/TEZ/D-IVA 43 [9.0%] subjects compared to ELX/TEZ/IVA 41 [8.4%] subjects). In addition, blood creatine phosphokinase elevations >5 x ULN were higher in subjects treated with VNZ/TEZ/D-IVA (38, 7.9%) compared to those treated with ELX/TEZ/IVA (32, 6.5%). The majority of AEs were mild to moderate. There were two SAEs, one in each treatment arm, leading to trial drug discontinuation and adjudicated as possibly related to trial drug. Both subjects had previously experienced elevations of creatine phosphokinase while on ELX/TEZ/IVA that were attributed to exercise. There were no cases of rhabdomyolysis reported.

6. Expected Postmarket Use

The prescribers of VNZ/TEZ/D-IVA are specialists in the care of CF and experienced in the use of other approved products in this class. The prescribers would include pulmonologists and other specialists who are part of the multidisciplinary clinical teams who manage patients with CF. As an orally administered drug, VNZ/TEZ/D-IVA will 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 did not propose any risk management activities for VNZ/TEZ/D-IVA beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of VNZ/TEZ/D-IVA on the basis of the efficacy and safety information currently available. The overall risk-benefit assessment supports the approval of VNZ/TEZ/D-IVA for the treatment of CF in patients aged 6 years and old with a copy of *F508del* or other responsive variants in the *CFTR* gene. Recently a Boxed Warning related to drug-induced liver injury and liver failure was added to the United States Prescribing Information (USPI) of ELX/TEZ/IVA following the identification of cases of liver failure leading to death or transplantation in patients without a history of liver disease. Based on the available information, there is no indication for a REMS at this time, however the serious risks for drug-induced liver injury and liver failure will be communicated through a boxed warning in approved product labeling. The risks will be followed through increased post-market surveillance through and enhanced pharmacovigilance strategy.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for VNZ/TEZ/D-IVA to ensure the benefits outweigh the risks. The FDA review team concludes that the benefit of VNZ/TEZ/D-IVA, based on noninferiority to ELX/TEZ/IVA as measured by pulmonary function, outweighs the risks when VNZ/TEZ/D-IVA is used as recommended in the approved labeling. The serious risks, including drug-induced liver injury and liver failure, will be communicated through approved product labeling. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

1. Vertex Pharmaceuticals. Proposed Alyftrek (Vanzacaftor,Tezacaftor, and Deutivacaftor Tablets) Prescribing Information. May 2, 2024.
2. Vertex Pharmaceuticals. Summary of Clinical Safety for Vanzacaftor,Tezacaftor, and Deutivacaftor, NDA 218730. May 2, 2024.

3. Vertex Pharmaceuticals. Safety Update for Vanzacaftor,Tezacaftor, and Deutivacaftor, NDA 218730. May 2, 2024.
4. Food and Drug Administration. Draft Integrated Review. NDA 218730 Vanzacaftor, Tezacaftor, and Deutivacaftor. November 16, 2024.
5. Katkin JP. Cystic fibrosis: Genetics and pathogenesis. In: UpToDate, Chmiel JF, Hoppin AG (Eds), UpToDate, Waltham, MA 2024.
6. Katkin JP. Cystic fibrosis: Clinical manifestations and diagnosis. In:UpToDate, Mallory GB, Hoppin AG (Eds), UpToDate, Waltham, MA 2019.
7. Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry. 2021 Annual Data Report. Bethesda, Maryland. ©2022 Cystic Fibrosis Foundation.
8. Vertex Pharmaceuticals. TRIKAFTA™ (elexacaftor, tezacaftor and ivacaftor tablets) Prescribing Information. October 2019.

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