CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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	219839
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Reviewer Name(s)	Stephanie Olumba, PharmD, MPH, BCPS
Team Leader(s)	Naomi Boston, PharmD
Acting Division Director	Laura Zendel, PharmD
Review Completion Date	June 24, 2025
Subject	Evaluation of Need for a REMS
[Established/Proper] Name	Sunvozertinib
Trade Name	Zegfrovy
Name of Applicant	Dizal (Jiangsu) Pharmaceutical Co., Ltd
Therapeutic Class	Kinase inhibitor
Dosage Form(s)	150 mg and 200 mg tablets
Dosing Regimen	200 mg orally once daily with food

Reference ID: 5613535

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Zegfrovy (sunvozertinib) is necessary to ensure the benefits outweigh its risks. Dizal (Jiangsu) Pharmaceutical Co., Ltd (Applicant) submitted a New Drug Application (NDA) 219839 for sunvozertinib with the proposed indication for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy. The risks associated with the use of sunvozertinib are interstitial lung disease/pneumonitis, gastrointestinal adverse reactions, dermatologic adverse reactions, ocular toxicity, and embryo-fetal toxicity. The Applicant did not submit a proposed REMS or risk management plan with this application.

DRM and Division of Oncology 2 (DO2) have determined that a REMS is not needed to ensure the benefits of sunvozertinib outweigh its risks. The clinical review team concluded that sunvozertinib benefit-risk profile is favorable and recommends accelerated approval for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy. The risks associated with sunvozertinib are considered acceptable in the context of a life-threatening condition and are similar to several FDA-approved treatments for NSCLC. The likely prescribers are oncologists who are expected to be familiar with managing the risks associated with sunvozertinib. The risks will be communicated in the Warnings and Precautions section of labeling.

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) Zegfrovy (sunvozertinib) is necessary to ensure the benefits outweigh its risks. Dizal (Jiangsu) Pharmaceutical Co., Ltd (Applicant) submitted a New Drug Application (NDA) 219839 for sunvozertinib with the proposed indication for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy. This application is under review in the Division of Oncology 2 (DO2). The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

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Sunvozertinib, a new molecular entity[a], is a kinase inhibitor of the epidermal growth factor receptor (EGFR). Sunvozertinib binds to and inhibits EGFR exon 20 insertion mutations at similar concentrations as wild-type EGFR. In cultured cell models, sunvozertinib inhibited EGFR phosphorylation in cells expressing different EGFR exon 20 insertion mutation variants at approximately 2- to 10-fold lower concentrations than wild-type EGFR signaling inhibition. Additionally, sunvozertinib exhibited anti-tumor activity against xenograft models of NSCLC with EGFR exon 20 insertion mutations.[1] The proposed indication for sunvozertinib is for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.[1]

Sunvozertinib is proposed to be supplied as tablets for oral administration in 150 mg and 200 mg dosage strengths. The proposed dosage for sunvozertinib is 200 mg orally once daily taken with food until disease progression or unacceptable toxicity.[b] Sunvozertinib was granted conditional approval by National Medical Products Administration (NMPA) in China on August 22, 2023 for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy, or who are intolerant to platinum-based chemotherapy.[2]

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 219839 relevant to this review:

- **01/26/2022**: Breakthrough therapy designation granted.
- **11/07/2024**: NDA 219839 submission received for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.
- **03/19/2025**: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that there are no major safety concerns identified at this time and there is currently no need for a REMS.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Lung cancer is one of the most common types of cancer and the leading cause of cancer-related deaths in the United Staes (US).[3] In 2025, The American Cancer Society estimates about 226,650 new cases of

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

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lung cancer and 124,730 deaths in the US.[c] Approximately 87% of all lung cancers cases are classified as NSCLC, which include subtypes such as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.[3,4] The 5-year relative survival rates for NSCLC depend on stage of diagnosis, ranging from 65% for local stage to 9% for distant stage.[5]

Screening for oncogenic driver mutations, such as EGFR mutations, is recommended in patients with advanced or metastatic NSCLC. EGFR mutations have been reported in approximately 15% of patients with NSCLC adenocarcinoma in the US.[6] These mutations are more prevalent in females and nonsmokers. Asian populations also have a high prevalence of EGFR mutations.[6] Furthermore, EGFR mutations comprise of multiple subtypes, such as exon 20 insertion mutations. EGFR exon 20 insertion mutations have been reported to account for 4% to 10% of all observed EGFR mutations in NSCLC.[7,d]

3.2. Description of Current Treatment Options

Treatment selection for patients with NSCLC typically depends on multiple factors such as stage at diagnosis, molecular characteristics, and patient's overall medical health.[4,8] Treatment options can include surgery, radiation therapy, chemotherapy, immunotherapy, or a combination of treatment modalities.[8] Targeted therapies may be used in patients with NSCLC who have driver mutations, such as EGFR gene mutations. Targeted therapies that are FDA-approved for common EGFR gene mutations (i.e., exon 19 deletions or exon 21 L858R substitution mutations) include osimertinib, amivantamab-vmjw plus lazertinib, and erlotinib.[9-12]

For patients with EGFR gene mutations with exon 20 insertion mutations, amivantamab-vmjw in combination with carboplatin and pemetrexed is approved for first-line treatment for adult patients with locally advanced or metastatic NSCLC. Amivantamab-vmjw is also approved for use as a single agent for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy.[9] Furthermore, a previously FDA-approved targeted therapy for EGFR exon 20 insertion mutation was withdrawn from the market. Mobocertinib is a kinase inhibitor that was granted accelerated approval on September 15, 2021, for the treatment of adult patients with locally advanced or metastatic NSCLC EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.[13] However, it was withdrawn from the market as of July 15, 2024 because the postmarketing trial did not verify clinical benefit.[14]

4. Benefit Assessment

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

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The efficacy of sunvozertinib was evaluated in study WU-KONG1B (NCT03974022), a multinational, open-label, dose randomization clinical study that included subjects with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations with disease progression on or after platinum-based chemotherapy and Eastern Cooperative Oncology Group (ECOG)[e] of score 0 or 1. Subjects with previously treated and stable intracranial metastases were eligible to enroll.[1] Subjects were excluded if they had spinal cord compression or leptomeningeal metastasis, past medical history of or clinically active interstitial lung disease, radiation related pneumonitis, or QTc interval > 470 msec. Women who were pregnant or breastfeeding were also excluded.[15] The median age of subjects was 61 years (range 35 to 88 years) and most (67%) were female. Sixty five percent of subjects were Asian, 33% were White, 2% were other races or had race not reported, and 2% were of Hispanic or Latino ethnicity. Additionally, 71% of subjects had never smoked. At baseline, 61% had ECOG performance status of 1; 96% had metastatic disease; 94% had adenocarcinoma histology; and 25% had brain metastases. All subjects had received prior platinum-based chemotherapy, 42% had received prior anti-PD-(L)1 therapy, and 14% had received prior amivantamab-vmjw.[1]

Subjects were randomized to receive either sunvozertinib 200 mg (n = 85) or sunvozertinib 300 mg (n = 89) orally once daily with food until disease progression or intolerable toxicity.[15] The primary efficacy outcome measure was overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 as evaluated by a blinded independent review committee (BIRC). An additional efficacy outcome measure was duration of response (DOR) by BIRC.

The ORR was 46% (95% CI:35, 57) for sunvozertinib 200 mg oral daily and the ORR was 46% (95% CI: 36, 56) for the sunvozertinib 300 mg oral daily. The median DOR was 11.1 months (95% CI: 8.3, NE) for sunvozertinib 200 mg once daily and 9.8 months (95% CI: 8.3, 13.9) for sunvozertinib 300 mg once daily.[15] (b) (4) (b) (4) (b) (4)[16] The efficacy results for sunvozertinib 200 mg are summarized in Table 1.[1]

Table 1: Efficacy Results of WU-KONG1B Study[1]

Efficacy Parameter	**Sunvozertinib 200 mg (N=85)**
Overall Response Rate (ORR), % (95% CI[a])	46 (35, 57)
Complete Response, %	6
Partial Response, %	40
Duration of Response (DOR)	**N=39**
Median[b], months (95% CI)	11.1 (8.2, NE)
Patients with DOR ≥6 months	72%
CI = confidence interval (b) (4)	

[e] The Eastern Cooperative Oncology Group (ECOG) performance status scale is a method to assess the functional status of a patient.

[a] 95% CI for ORR was calculated based on Clopper-Pearson exact CI method
[b] Kaplan-Meier estimate using confirmed responses

The clinical review team concluded that the efficacy results for sunvozertinib 200 mg once daily supports accelerated approval for the treatment in adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.[f] Refer to the FDA Multidisciplinary Review and Evaluation: NDA 219839 Zegfrovy (sunvozertinib) for more information.[15]

5. Risk Assessment & Safe-Use Conditions

The pooled safety population included 121 subjects with locally advanced or metastatic NSCLC that received sunvozertinib 200 mg from study WU-KONG1 (n=118) and from study WU-KONG2 (n=3). WU-KONG2 was a phase 1 study to assess the safety, tolerability, pharmacokinetics, and anti-tumor efficacy of sunvozertinib in Chinese NSCLC patients with EGFR or HER2 mutations. Among the 121 subjects that that received sunvozertinib 200 mg, 56% of subjects were exposed for 6 months or longer and 28% of subjects were exposed for greater than one year.[1]

The most common adverse reactions were diarrhea, rash, decreased appetite, stomatitis, fatigue, paronychia, vomiting, nausea, constipation, musculoskeletal pain, pruritus, dry skin, urinary tract infection, abdominal pain, and decreased weight. The most frequent Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, increased lipase, decreased hemoglobin, increased amylase, increased creatine kinase, decreased neutrophils, decreased potassium, increased aspartate aminotransferase, increased alanine aminotransferase, decreased sodium, increased magnesium, and increased alkaline phosphatase.[1]

In study WU-KONG1B, serious adverse reactions occurred in 41% of subjects treated with sunvozertinib. The most common serious adverse reactions that occurred ≥2% were pneumonia (7%), dyspnea (4.4%), and rash (2.2%). Adverse reactions leading to treatment discontinuation occurred in 8% of subjects. The adverse reactions leading to treatment discontinuation included pneumonia and rash (2.2% each). Additionally, 48% of subjects that experienced adverse reactions leading to dose interruption. Adverse reactions leading to dose interruption included vomiting (9%) and rash (8%). Dose reduction of sunvozertinib due to adverse reactions occurred in 23% of subjects. Adverse reactions requiring dose reduction included rash (4.4%) and diarrhea (3.3%). Fatal adverse reactions occurred in 2.2% of subjects who received sunvozertinib including thrombosis (1.1%) and COVID-19 infection (1.1%).[1]

The Warnings and Precautions section of the proposed label include the risks of interstitial lung disease/pneumonitis, gastrointestinal adverse reactions, dermatologic adverse reactions, ocular toxicity,

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

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and embryo-fetal toxicity.[g] At the time of this review, labeling negotiations were ongoing with the Applicant.

5.1. Interstitial Lung Disease/Pneumonitis

Interstitial lung disease/pneumonitis can be life-threatening and occurred in sunvozertinib safety population. Interstitial lung disease/pneumonitis occurred in 1.7% of subjects, and 0.8% of subjects discontinued sunvozertinib due to interstitial lung disease/pneumonitis. The median time to first onset for interstitial lung disease/pneumonitis was 61 days (range 35 to 86 days).

The Warnings and Precautions of the proposed label advises healthcare providers to monitor patients for new or worsening pulmonary symptoms indicative of interstitial lung disease/pneumonitis (e.g., dyspnea, cough, and fever). Healthcare providers should immediately withhold sunvozertinib in patients with suspected interstitial lung disease /pneumonitis and permanently discontinue sunvozertinib if interstitial lung disease/pneumonitis is confirmed.

5.2. Gastrointestinal Adverse Reactions

Serious gastrointestinal adverse reactions, such as diarrhea and nausea, occurred in 1.7% of subjects, including 0.8% Grade 3 nausea. Diarrhea occurred in 73% of subjects who received sunvozertinib, including 2.5% of subjects with Grade 3. Diarrhea leading to dosage interruption or dose reduction occurred in 5% of subjects, 0.8% of subjects required permanent discontinuation of sunvozertinib. Nausea and vomiting occurred in 43% of subjects, including 3.3% Grade 3 events. Nausea and vomiting leading to dosage interruption or dose reduction occurred in 7% of subjects and permanent discontinuation of sunvozertinib occurred in 0.8% of subjects.

The Warnings and Precautions of the proposed label advises healthcare providers to administer sunvozertinib with food to reduce gastrointestinal adverse reactions. Healthcare providers should monitor patients for gastrointestinal toxicity, and provide supportive care, including anti-diarrheal, anti-emetics, or fluid replacement, as indicated. Healthcare providers should withhold, reduce the dose, or permanently discontinue sunvozertinib based on severity.

5.3. Dermatologic Adverse Reactions

Sunvozertinib can cause severe rash including acneiform dermatitis and pruritis. In the safety population, dermatologic adverse reactions occurred in 68% of subjects including 9% acneiform dermatitis. Grade 3 dermatologic adverse reactions were 7% rash, 0.8% acneiform dermatitis, and 0.8% pruritus.

[g] Section 505-1 (a) of the FD&C Act: *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.*

The Warnings and Precautions of the proposed label advises healthcare providers to instruct patients to use alcohol-free (e.g., isopropanol-free, ethanol-free) emollient cream during treatment with sunvozertinib and to avoid the use of irritating skin products (e.g., products containing retinol or retinoic acid, benzoyl peroxides). Healthcare providers should withhold, reduce the dose, or permanently discontinue sunvozertinib based on severity.

5.4. Ocular Toxicity

Sunvozertinib can cause ocular toxicity including keratitis, dry eye symptoms, blurred vision, and visual impairment. Based on the safety population, ocular toxicity occurred in 13% of subjects who received sunvozertinib, including keratitis (0.8%).

The Warnings and Precautions of the proposed label instructs healthcare providers to promptly refer patients with new or worsening eye symptoms to an ophthalmologist. Healthcare providers should advise discontinuation of contact lenses until ocular symptoms are evaluated. Healthcare providers should withhold, reduce the dose, or permanently discontinue sunvozertinib based on severity.

5.5. Embryo-Fetal Toxicity

Based on the mechanism of action and findings from animal studies, sunvozertinib can cause fetal harm when administered to pregnant woman. In animal reproduction studies, oral administration of sunvozertinib to pregnant animals during the period of organogenesis resulted in structural abnormalities at concentrations below the human exposure at the highest recommended dose based on area under the curve.

The Warnings and Precautions of the proposed label instructs healthcare providers to advise pregnant women and females of reproductive potential of the potential risk to a fetus. Healthcare providers should advise females of reproductive potential to use effective non-hormonal contraception during treatment with sunvozertinib and for 2 weeks after the last dose, since sunvozertinib can render some hormonal contraceptives ineffective. The proposed label instructs healthcare providers to advise male patients with female partners of reproductive potential to use effective contraception during treatment with sunvozertinib and for 2 weeks after the last dose.

6. Expected Postmarket Use

Sunvozertinib is expected to be primarily prescribed in both inpatient and outpatient oncology settings. The likely prescribers of sunvozertinib are oncologists who are expected to be familiar with managing the risks associated with sunvozertinib, as other drug products used in the treatment of NCSLC share similar risks.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for sunvozertinib beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The clinical review team recommends accelerated approval of sunvozertinib on the basis of the efficacy and safety information currently available for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy. Under the accelerated approval, the Applicant will be required to verify clinical benefit of sunvozertinib with a postmarketing randomized trial.

The serious risks associated with sunvozertinib are interstitial lung disease/pneumonitis, gastrointestinal adverse reactions, dermatologic adverse reactions, ocular toxicity, and embryo-fetal toxicity. The clinical review team concluded that the risks of sunvozertinib are considered acceptable in the context of a life-threatening condition. These risks are similar with several FDA-approved treatments for NSCLC. For instance, amivantamab-vmjw, lazertinib, and ensartinib are associated with interstitial lung disease/pneumonitis, dermatologic adverse reactions, and embryo-fetal toxicity.[9,11,17] Additionally, adagrasib and ceritinib are associated with gastrointestinal adverse reactions;[18,19] and amivantamab-vmjw, lazertinib, and afatinib are associated with ocular toxicity or keratitis.[9,11,20] None of these products are approved with a REMS, and the risks are communicated through the Warnings and Precautions section of labeling.

The likely prescribers are oncologists who are expected to be familiar with managing the risks associated with sunvozertinib. Based on the available data, DRM and DO2 have determined that a REMS is not necessary to ensure the benefits of sunvozertinib outweigh the risks. If sunvozertinib is approved, these risks will be communicated in the Warnings and Precautions section of labeling.

9. Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits outweigh the risks of sunvozertinib. 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.

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STEPHANIE N OLUMBA
06/24/2025 01:07:59 PM

NAOMI S BOSTON
06/24/2025 03:19:53 PM

LAURA A ZENDEL
06/24/2025 04:04:51 PM