CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218213Orig1s000

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	218213
PDUFA Goal Date	November 27, 2023
OSE RCM #	2023-4197; 2023-4199
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Deputy Director	Laura Zendel, Pharm.D.
Review Completion Date	November 13, 2023
Subject	Evaluation of the need for a REMS
Established Name	Repotrectinib
Trade Name	Augtyro
Name of Applicant	Bristol Myers Squibb Co.
Therapeutic Class	Kinase inhibitor
Formulation(s)	40mg gelatin capsules
Dosing Regimen	160 mg orally once daily for 14 days, then increase to 160 mg twice daily

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for repotrectinib is necessary to ensure the benefits outweigh its risks. Bristol Myers Squibb Co. submitted a New Drug Application (NDA) 218213 for repotrectinib with the proposed indication for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC). The serious risks associated with the use of repotrectinib are central nervous system (CNS) adverse reactions, interstitial lung disease (ILD)/pneumonitis, hepatotoxicity, myalgia with creatine phosphokinase (CPK) elevation, hyperuricemia, skeletal fractures, and embryo-fetal toxicity. The Applicant did not submit a REMS or risk management plan with this application.

The Division of Risk Management (DRM) and the Division of Oncology 2 (DO2) have determined that a REMS is not necessary to ensure the benefits of repotrectinib outweigh its risks. Based on the efficacy and safety information currently available, the clinical reviewer stated that repotrectinib shows clinically meaningful benefit and recommends approval of repotrectinib as a kinase inhibitor indicated for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive NSCLC. The review team concluded that the treatment with repotrectinib demonstrated a clinically meaningful and durable overall response rate (ORR) among adult patients with locally advanced or metastatic ROS1-positive NSCLC in the in the tyrosine kinase inhibitor (TKI)-naïve population, in the TKI-pretreated population, and in patients with resistance mutations. The safety profile is similar to other TKIs approved for similar indications which do not require a REMS. If approved, labeling will be similar to the currently approved other TKIs, such as crizotinib (Xalkori), and entrectinib (Rozlytreck). Management of the adverse events of repotrectinib will be communicated in Warnings and Precautions, Patient Counseling Information, and the Patient Package Insert (PPI).

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for repotrectinib is necessary to ensure the benefits outweigh its risks. Bristol Myers Squibb Co. submitted a New Drug Application (NDA) 218213 for repotrectinib with the proposed indication for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC).[1] This application is under review in the Division of Oncology 2 (DO2). The applicant did not submit a REMS or risk management plan with this application.

2 Background

2.1 Product Information

Repotrectinib is a new molecular entity (NME) NDA type 505(b)(1) pathway application.[a] This product is an inhibitor of proto-oncogene tyrosine-protein kinase *ROS1 (ROS1)* and of the tropomyosin receptor tyrosine kinases (TRKs) TRKA, TRKB, and TRKC. Fusion proteins that include ROS1 domains can drive tumorigenic potential through hyperactivation of downstream signaling pathways leading to unconstrained cell proliferation.[1] Repotrectinib is proposed to be supplied as 40 mg hard gelatin capsules. The recommended dosage of repotrectinib is 160 mg orally once daily for 14 days, then

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

increase to 160 mg twice daily until disease progression or unacceptable toxicity.[b,1] Repotrectinib was granted fast track and breakthrough therapy designations for multiple indications. Repotrectinib is not currently approved in any jurisdiction.

2.2 Regulatory History

The following is a summary of the regulatory history for repotrectinib (NDA 218213) relevant to this review:

- 09/30/2016: Investigation New Drug (IND) 130465 submission for repotrectinib (TPX-0005) received.
- 12/16/2019: Fast track designation granted for the treatment of patients with ROS1-positive advanced NSCLC who have had disease progression following one prior line of platinum-based chemotherapy and one prior line of a ROS1 tyrosine kinase inhibitor (TKI).
- 05/12/2020: Fast track designation granted for the treatment of patients with ROS1-positive advanced NSCLC who have not been treated with a ROS1 TKI.
- 08/21/2020: Fast track designation granted for the treatment of patients with advanced solid tumors that have an NTRK gene fusion who have progressed following treatment with at least one prior line of chemotherapy and one or two prior TRK tyrosine kinase inhibitors and have no satisfactory alternative treatments.
- 12/07/2020: Breakthrough therapy designation granted for the treatment of patients with ROS1-positive metastatic NSCLC who have not been treated with a ROS1 TKI.
- 08/10/2021: Fast track designation granted for the treatment of patients with ROS1-positive advanced NSCLC who have been previously treated with one ROS1 TKI and who have not received prior-platinum-based chemotherapy.
- 05/09/2022: Breakthrough therapy designation granted for treatment of patients with ROS1-positive metastatic NSCLC who have been previously treated with one ROS1 TKI and who have not received prior platinum-based chemotherapy.
- 03/27/2023: NDA 218213 submission for repotrectinib with the proposed indication for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive NSCLC, received.
- 08/07/2023: The Agency informed the Applicant via Mid-Cycle Communication Agenda that based on the currently available data, there were no safety issues that require a REMS for repotrectinib.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Lung cancer is the most common cause of cancer death worldwide, with an estimated 1.6 million deaths each year. Approximately 85% of patients have a group of histological subtypes collectively known as

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

NSCLC, of which lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) are the most common subtypes.[2] Lung cancer is the second most common cancer and the leading cause of cancer death in the USA. The greatest risk factor for development of lung cancer is tobacco use. Secondhand smoking has also been shown to increase the risk of lung cancer by as much as 26%. Other risk factors for lung cancer include asbestos exposure, family history of lung cancer, exposure to toxic substances including polycyclic aromatic hydrocarbons, heavy metals, and radon gas.[3] The expected number of new cases of lung and bronchus cancer in the United States in 2023 is 238,340[c], with 127,070 expected deaths due to the disease[d].[4] Five-year survival for patients diagnosed with lung and bronchus cancer is approximately 25.4%.[5] It is now recognized that a significant proportion of these NSCLC patients present alterations in certain genes that drive oncogenesis, including *KRAS*, *EGFR*, *BRAF*, *MET*, *HER2*, *ALK*, *ROS1*, and *NTRK*, among others.[6] ROS-1 rearrangement is found in 0.9–2.6% of NSCLCs mostly lung adenocarcinomas, with a significantly higher rate of women, non-smokers, and a tendency to a younger age. ROS-1-positive NSCLCs are predominantly lepidic, acinar, or solid adenocarcinomas, with more than 90% expressing thyroid transcription factor-1 (TTF1), diagnosed at an advanced stage (stage III – IV), with a higher frequency of brain metastases. A heightened thromboembolic risk of ROS-1-rearranged tumors compared with NSCLCs harboring non-rearranged ROS-1, and even rarer cases of thrombotic microangiopathies and disseminated intravascular coagulation.[7]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Depending on the stage, histology, genetic alterations, and patient's condition, the treatment approaches in NSCLC usually include surgery, radiotherapy, chemotherapy, immunotherapy, molecularly targeted therapy either alone or in combined modality.[3] Chemotherapy remained a standard treatment for *ROS1*-positive NSCLC until approval of targeted therapies. The National Comprehensive Cancer Network (NCCN) panel recommends four agents for patients with ROS1-positive metastatic NSCLC—ceritinib, crizotinib, entrectinib, and lorlatinib. Based on clinical trial data and FDA approvals, the panel determined that crizotinib[8] and entrectinib[9] are preferred first-line therapy options for patients with ROS1-positive metastatic NSCLC because they are better tolerated, have been assessed in more patients, and are approved by the FDA for ROS1-positive NSCLC.[10] Crizotinib was approved as first line therapy for ROS-1-positive NSCLC in 2016 by the Food Drug Administration (FDA) and, and entrectinib was approved for the same indication by the FDA in 2019.[11] None of these products have a boxed warning in their labels, nor was a REMS required for approval. Ceritinib is active in crizotinib-naive ROS1-rearranged NSCLC; however, its toxicity profile and lack of regulatory approval make it a less compelling option.[12] Lorlatinib is a third-generation oral TKI that targets ALK and ROS1 tyrosine kinases and has good CNS penetration. The NCCN NSCLC Panel recommends lorlatinib as a subsequent therapy option for select patients with ROS1-positive metastatic NSCLC and disease progression after treatment with ceritinib, crizotinib, or entrectinib, depending on the type of progression. Entrectinib is recommended as subsequent therapy for patients with CNS progression after crizotinib or ceritinib.[10]
There are currently no approved targeted therapies indicated for advanced *ROS1*-positive NSCLC patients previously treated with first line ROS1 TKI treatment (ie, crizotinib or entrectinib). Despite crizotinib's efficacy, there are several ways ROS1-rearranged NSCLC can develop resistance to it. ROS1

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

[d] 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.*

rearrangements can be pressured to develop secondary ROS1 resistance mutations (on-target) or alternative bypass pathways (off-target) that can lead to downstream signaling and cell proliferation. The most common resistance mutations in ROS1-rearranged NSCLC were G2032R (41%), D2033N (6%), and S1986F (6%). As of today, there are no FDA-approved TKIs that can overcome the G2032R mutation. Therapies that are recommended and used in this setting include platinum-based chemotherapy and lorlatinib; however, neither treatment option is FDA approved in this setting. Please refer DO2's Multi-disciplinary Review and Evaluation (draft) for repotrectinib for a detailed clinical review on treatment armamentarium relevant to the proposed indication.[13] Although multiple next-generation TKIs are under investigation, chemotherapy is the current treatment of choice for these patients.[12] It remains a high unmet medical need for the TKI-pretreated population for which there is no approved targeted therapy, and no approved agent with clinical activity in patients who have developed an acquired resistant mutation.

4 Benefit Assessment

The efficacy of repotrectinib was evaluated in TRIDENT-1, a multicenter, single-arm, open-label, multi-cohort clinical trial (NCT03093116). The efficacy populations included 71 ROS1 TKI-naïve patients who received up to 1 prior line of platinum-based chemotherapy and/or immunotherapy and 56 patients who received 1 prior ROS1 TKI with no prior platinum-based chemotherapy or immunotherapy. Among the 71 ROS1 TKI-naïve patients, the median age was 57 years (range: 28 to 80); at baseline, 94.4% patients had metastatic disease, 25.4% patients had CNS metastases by blinded independent central review (BICR); 97.2% had adenocarcinoma; and 28.2% patients had prior chemotherapy consisting of platinum-based chemotherapy and/or immunotherapy for locally advanced or metastatic disease. Among the 56 patients who had received 1 prior ROS1 TKI (crizotinib 82%, entrectinib 16%, and ceritinib 2%) with no prior platinum-based chemotherapy or immunotherapy, the median age was 57 years (range: 33 – 78); at baseline, 98.2% patients had metastatic disease, 42.9% with CNS metastases by BICR, and 94.6% had adenocarcinoma. Eligible patients were required to have *ROS1*-positive locally advanced or metastatic NSCLC, ECOG performance status ≤1, measurable disease per RECIST v 1.1, and ≥8 months from first dose. All patients were assessed for CNS lesions at baseline, and patients with symptomatic brain metastases were excluded from the trial. Patients received repotrectinib 160 mg orally once daily for 14 days, then increased to 160 mg twice daily until disease progression or unacceptable toxicity. Tumor assessments were performed at least every 8 weeks. Identification of *ROS1* gene fusions in tumor specimens was prospectively determined in local laboratories using next-generation sequencing (NGS), polymerase chain reaction (PCR) or fluorescence in situ hybridization (FISH) tests. All *ROS1*-positive patients by local FISH testing required central laboratory confirmation of *ROS1* fusion using an analytically validated NGS test. *ROS1* fusions were identified by NGS in 51%, FISH in 26%, and PCR in 23%. Efficacy was established based on overall response rate (ORR) and duration of response (DOR) according to RECIST v1.1 as assessed by BICR. Intracranial response according to modified RECIST v1.1 was assessed by BICR. Tumor assessments with imaging were performed every 8 weeks. The efficacy results are summarized in Table 1.[1,13,e]

[e] 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*

Table 1: Efficacy Results for Patients with *ROS1*-Positive NSCLC in TRIDENT-1[1,13,e]

Efficacy Parameters	ROS1 Inhibitor Naïve Patients (N=71)	ROS1 Inhibitor Pretreated Patients (N=56)
Confirmed Overall Response Rate, % (95% CI)	79% (68, 88)	38% (25, 52)
Complete Response	6%	5%
Partial Response	73%	32%
Duration of Response (DOR)[a]		
Median in Months (95% CI)[b]	34.1 (25.6, NE)	14.8 (7.6, NE)
Range (months)	1.4+, 42.4+	3.6, 22.9+
% DOR ≥12 months[c]	70	48

Abbreviations: CI = confidence interval; NE = not evaluable; "+" indicates ongoing response

[a] DOR results are based on the updated data as of 19 December 2022

[b] Median DOR (95% CI) are based on Kaplan-Meier estimates

[c] DOR landmark analysis is based on the observed DOR.

In the pooled population of TKI-Naïve subjects with *ROS1*-positive NSCLC (N = 71), treatment with repotrectinib demonstrated clinically meaningful efficacy through an anti-tumor activity with a confirmed ORR by BICR of 79% (N = 56 of 71; 95% CI: 68, 88), with median time to response of 1.8 months (range 0.9 to 5.5 months). Durable responses with an estimated median DOR of 34.1 months (95% CI: 26, NE), with landmark analyses of DOR showing a probability of subjects remaining in a response at ≥ 12 months was 70% (b) (4)

In the pooled population of TKI-pretreated subjects with *ROS1*-positive NSCLC (N = 56), treatment with repotrectinib demonstrated clinically meaningful efficacy through a clinically meaningful activity with a confirmed ORR by BICR of 38% (N = 21 of 56; 95% CI: 25, 52), with median time to response of 1.8 months (range 1.6 to 3.6 months). Durable responses with an estimated median DOR of 14.8 months (95% CI: 7.6, NE), with landmark analyses of DOR showing a probability of subjects remaining in a response at ≥ 12 months was 48%. (b) (4)

The clinical reviewer stated that the submitted evidence meets the statutory evidentiary standard for traditional approval. Treatment with repotrectinib demonstrated a clinically meaningful and durable ORR among adult patients with locally advanced or metastatic ROS1-positive NSCLC in the in the TKI-naïve population, in the TKI-pretreated population, and in patients with resistance mutations.[1,13,e]

5 Risk Assessment & Safe-Use Conditions

The following section is a summary of relevant safety information to date for repotrectinib. The safety of repotrectinib was evaluated in 264 patients with ROS1 positive NSCLC in TRIDENT-1. (see Section 4: Benefit Assessment). Patients with a history of ILD, drug-related pneumonitis, significant, uncontrolled,

active cardiovascular disease, or prolonged QTc interval were excluded from enrollment in this trial. Among patients who received repotrectinib, 52% were exposed for at least 6 months, and 27% were exposed for greater than one year.[1]

The pooled safety population (n=351) reflects the exposure to repotrectinib as a single-agent, dosed at 160 mg orally once daily for 14 days, then increased to 160 mg twice daily until disease progression or unacceptable toxicity with ROS1-positive NSCLC and other solid tumors in the TRIDENT-1 trial, (b) (4) Among these 351 patients, 52% were exposed for 6 months or longer and 26% were exposed for greater than one year. In this pooled safety population, the most common (≥ 20%) adverse reactions were dizziness (64%), dysgeusia (50%), peripheral neuropathy (47%), constipation (37%), dyspnea (30%), ataxia (29%), fatigue (29%), cognitive disorders (23%) and nausea (20%). The most common (≥2%) Grade 3 or 4 laboratory abnormalities were increased gamma glutamyl transferase (13%), decreased lymphocytes (10%), increased urate (10%), decreased neutrophils (8%), decreased hemoglobin (7%), increased creatine phosphokinase (5.8%), decreased phosphate (4.9%), decreased leukocytes (3.8%), increased ALT (3.5%), decreased sodium (3.5%), increased AST (2.9%), increased magnesium (2.9%), increased alkaline phosphatase (2.6%), and increased glucose (2%).[1]

Deaths

Fatal adverse reactions were reported in 4.2% of patients who received repotrectinib, including death, pneumonia, pneumonia aspiration, cardiac arrest, sudden cardiac death, cardiac failure, sudden death, hypoxia, dyspnea, respiratory failure, tremor, and disseminated intravascular coagulation.[1] There were no reported TEAEs with a fatal outcome assessed as treatment related by the Investigator. All other deaths were attributed to progressive disease by the Investigator, which included 37 (8.3%) deaths attributed to progressive disease that were reported as occurring within 28 days of the last dose of repotrectinib. Overall, the deaths reported across the repotrectinib clinical program are consistent with the seriousness, complications and/or progression of the underlying malignancy, and life-threatening nature of disease under investigation.[13]

Serious Adverse Reactions

Serious adverse reactions were reported in 33% of patients who received repotrectinib. Serious adverse reactions reported in ≥2% of patients included pneumonia (5.7%), dyspnea (3.8%), pleural effusion (3.4%), and hypoxia (3.0%). Permanent discontinuation of repotrectinib occurred in (b) (4) of patients due to adverse reactions. Adverse reactions which resulted in permanent discontinuation of repotrectinib reported in at least ≥1% of patients included were dyspnea, pneumonitis, and muscular weakness. Dosage interruptions of repotrectinib due to an adverse reaction occurred in 48% of patients. Adverse reactions that required dosage interruption in ≥5% of patients included dyspnea, and muscular weakness. Dose reductions of repotrectinib due to an adverse reaction occurred in 35% of patients. Adverse reactions that required dosage reductions in ≥5% of patients included dizziness.[1]

Similar to other TKIs, such as crizotinib (Xalkori)[8], and entrectinib (Rozlytreck)[9], if approved, labeling will include the following risks in the Warnings and Precautions section.

5.1 CENTRAL NERVOUS SYSTEM (CNS) ADVERSE REACTIONS (AES)

In the pivotal clinical trial, CNS AEs including dizziness, ataxia, and cognitive disorders were reported in 75% with Grade 3 or 4 events occurring in 4% among the 351 patients who received repotrectinib. Dizziness including vertigo was reported in 64% of patients; Grade 3 dizziness was reported in 2.8% of patients. The median time to onset was 6 days (1 day to 1.4 years). Dose interruption was required in (b) (4) of patients and (b) (4) required dose reduction due to dizziness.[1]

Ataxia, including gait disturbance and balance disorder, occurred in in 29% of the 351 patients; ≥ Grade 3 ataxia was reported in 0.3% of patients. The median time to onset was 15 days (1 day to 1.4 years). Dose interruption was required in 6% of patients, 8% required dose reduction and one patient (0.3%) permanently discontinued repotrectinib due to ataxia.[1]

Cognitive disorders, including memory impairment and disturbance in attention, were reported in 23% of the 351 patients. Cognitive disorders included memory impairment (13%), disturbance in attention (11%), and confusional state (2%); Grade 3 cognitive disorders occurred in 0.9% of patients. The median time to onset of cognitive disorders was 37 days (1 day to 1.4 years). Dose interruption was required in 2% of patients, 1.7% required dose reduction and 0.6% patients permanently discontinued repotrectinib due to cognitive adverse reactions.[1]

Mood disorders occurred in 6% of the 351 patients. Mood disorders occurring in > 1% of patients included anxiety (2.8%), irritability (1.1%), and depression (1.4%); Grade 4 mood disorders (mania) occurred in 0.3% of patients. Dose interruption was required in 0.3% of patients and 0.3% of patients required a dose reduction due to mood disorders.[1]

Sleep disorders including insomnia and hypersomnia occurred in 15% of the 351 patients. Sleep disorders observed in > 1% of patients were somnolence (8%), insomnia (6%) and hypersomnia (1.1%). Dose interruption was required in 0.9% of patients and 0.3% of patients required a dose reduction due to sleep disorders.[1]

Labeling instructs to advise patients and caregivers of the risk of CNS adverse reactions, and to advise patients not to drive or use machines if they are experiencing CNS adverse reactions. Monitoring and dosage modifications for toxicities to address the safety issues with repotrectinib will also be included in the Dosage and Administration section of the label.[1]

5.2 INTERSTITIAL LUNG DISEASE (ILD)/PNEUMONITIS

In the clinical trial, ILD/pneumonitis (pneumonitis [2.6%] and interstitial lung disease [0.3%]) was reported in 2.9% of patients; Grade 3 ILD/pneumonitis was reported in 1.1% of patients, among the 351 patients treated with repotrectinib. The median time to onset was 45 days (19 days to 0.9 years). Dose interruption was required in 1.4% of patients, 0.6% of patients required dose reduction, and 1.1% patients permanently discontinued repotrectinib due to ILD/pneumonitis. Labeling instructs to monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis, and advise to immediately withhold repotrectinib in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed. Monitoring and dosage modifications for toxicities to address the safety issues with repotrectinib will also be included in the Dosage and Administration section of the label.[1]

5.3 HEPATOTOXICITY

In the clinical trial, among the 351 patients treated with repotrectinib, any grade increases of ALT (35%) and AST (40%) with Grade 3 or 4 ALT (2%) and AST (2.6%), respectively, were reported. The median time to onset of increased hepatic enzymes was 15 days (range: 1 day to 1.9 years). Increased ALT or AST leading to dose interruptions or reductions occurred in 2.8% and 1.4% of patients, respectively. Hyperbilirubinemia leading to dose interruptions occurred in 0.6%. Labeling instructs to monitor liver function, including ALT, AST and bilirubin, every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated. Labeling also instructs to withhold and then resume at same or reduced dose upon improvement or permanently discontinue repotrectinib based on the severity. Monitoring and dosage modifications for toxicities to address the safety issues with repotrectinib will also be included in the Dosage and Administration section of the label. [1]

5.4 MYALGIA WITH CREATINE PHOSPHOKINASE (CPK) ELEVATION

Myalgia (b) (4) occurred in 13% with Grade 3 (0.6%) among the 351 patients treated with repotrectinib. Median time to onset of myalgia was 19 days (range: 1 day to 2 years). Concurrent increased CPK within 7-day window was observed in 3.7% of patients. Repotrectinib was interrupted in one patient with myalgia and concurrent CPK elevation. Labeling instructs to advise patients to report any unexplained muscle pain, tenderness, or weakness. Labeling instructs healthcare providers to monitor serum CPK levels during the repotrectinib treatment and monitor CPK levels every 2 weeks during the first month of treatment and as needed in patients reporting unexplained muscle pain, tenderness, or weakness. Monitoring and dosage modifications for toxicities to address the safety issues with repotrectinib will also be included in the Dosage and Administration section of the label.[1]

5.5 HYPERURICEMIA

In the clinical trial, hyperuricemia reported as adverse reactions occurred in 5% and Grade 3 or 4 occurred in 0.9% among the 351 patients treated with repotrectinib. One patient without pre-existing gout required urate lowering medication. Labeling instructs healthcare providers to monitor serum uric acid levels prior to initiating repotrectinib and periodically during treatment, and to initiate treatment with urate-lowering medications as clinically indicated. Monitoring and dosage modifications for toxicities to address the safety issues with repotrectinib will also be included in the Dosage and Administration section of the label.[1]

5.6 SKELETAL FRACTURES

In the clinical trial, among 351 adult patients who received repotrectinib, fractures occurred in 2.3%. Fractures involved the spine (0.3%), ribs (0.6%), acetabulum (0.3%), feet (0.6%), sternum (0.3%), and ankles (0.3%). Some fractures occurred at sites of disease and prior radiation therapy. The median time to fracture was 71 days (range: 31 days to 1.4 years). Repotrectinib was interrupted in 0.3% of patients.Labeling instructs healthcare providers to promptly evaluate patients with signs or symptoms (e.g., pain, changes in mobility, deformity) of fractures.

5.7 EMBRYO-FETAL TOXICITY

Based on its mechanism of action and findings from animal data, repotrectinib can cause fetal harm when administered to a pregnant woman. Oral administration of repotrectinib to pregnant rats during

the period of organogenesis resulted in fetal malformations at doses approximately 0.3 times the recommended 160 mg twice daily dose based on body surface area (BSA). Labeling instructs healthcare providers to advise pregnant women of the potential risk to a fetus. Besides being communicated in the Warnings and Precautions section of the label, recommended guidance to use effective non-hormonal contraception during treatment with repotrectinib and for 2 months after the last dose for females of childbearing potential and to use effective contraception during treatment with repotrectinib and for 4 months following the last dose for male patients with female partners of childbearing potential, will be communicated in the Use in Specific Populations section of the label.[1]

6 Expected Postmarket Use

Similar to other TKIs, if approved, repotrectinib will be administered in both inpatient and outpatient settings. It is expected that oncologists, familiar with the management of toxicities such as CNS adverse reactions, ILD/pneumonitis, hepatotoxicity, myalgia with CPK elevation, hyperuricemia, skeletal fractures, and embryo-fetal toxicity, will be the likely prescribers of repotrectinib.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not submit any risk management activities for repotrectinib beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for repotrectinib, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the likely prescribing population.

Repotrectinib is a kinase inhibitor, with the proposed indication for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive NSCLC. NSCLC represents approximately 85% of all lung cancer. Lung cancer is the second most common cancer and the leading cause of cancer death in the USA. Despite the use of therapies targeted towards ROS1-positive NSCLC, there are several ways ROS1-rearranged NSCLC can develop resistance to it. Although multiple next-generation TKIs are under investigation, chemotherapy is the current treatment of choice for these patients.[12] It remains a high unmet medical need for the TKI-pretreated population for which there is no approved targeted therapy, and no approved agent with clinical activity in patients who have developed an acquired resistant mutation. Based on the efficacy and safety information currently available, the clinical reviewer stated that repotrectinib shows clinically meaningful benefit and recommends approval of repotrectinib as a kinase inhibitor indicated for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive NSCLC.[1,13] Repotrectinib appeared efficacious in its primary outcome of ORR and secondary outcome of DOR, and its risks can be communicated and managed through labeling.[1,13] The clinical reviewer stated that the treatment with repotrectinib demonstrated a clinically meaningful and durable ORR among adult patients with locally advanced or metastatic ROS1-positive NSCLC in the in the TKI-naïve population, in the TKI-pretreated population, and in patients with resistance mutations. Therefore, the review team recommends granting line agnostic approval to repotrectinib for the treatment of patients with locally advanced or metastatic ROS1-positive NSCLC.[13]

DRM and DO2 have determined that if approved, a REMS is not necessary to ensure the benefits of repotrectinib outweigh its risks. The most concerning adverse reactions observed with the use of repotrectinib are risks for CNS adverse reactions, ILD/pneumonitis, hepatotoxicity, myalgia with CPK elevation, hyperuricemia, vision disorders, skeletal fractures, and embryo-fetal toxicity, which are the same as in the currently approved TKIs, such as crizotinib (Xalkori)[8], and entrectinib (Rozlytreck)[9]. It is expected that oncologists, familiar with the management of these toxicities, will be the likely prescribers of repotrectinib. The review team concluded the observed safety profile is acceptable when assessed in the context of a life-threatening disease.[13] None of the approved TKIs have a boxed warning in their labels, nor was a REMS required for approval. At the time of this review, none of the risks associated with repotrectinib will receive a boxed warning in the label.[1] If repotrectinib is approved, similar to the approved TKIs, such as crizotinib (Xalkori), and entrectinib (Rozlytreck), Warnings and Precautions in the labeling will be used to communicate the safety issues and management of toxicities associated with repotrectinib, as well as information to be included in Patient Counseling Information, and in the PPI.

Additionally, to better characterize safety the Agency is planning to issue a post-marketing required (PMR) study to evaluate the risk factors, manifestations, and outcomes of ocular toxicity associated with repotrectinib in a sufficient number of patients with ROS1 positive NSCLC or other solid tumors to assess the risk of serious ocular toxicity, and one post-marketing commitment (PMC) will be issued to ensure development of a companion diagnostic test. A second PMC, to provide updated ORR and DOR results for the patients with ROS1-positive NSCLC in the primary efficacy evaluable populations in TRIDENT-1 (patients naïve to ROS1 TKIs and those who are ROS1 TKI-pretreated), after patients have been followed for at least 18 months from the date of initial response.[14]

9 Conclusion & Recommendations

DRM has determined that a REMS is not necessary to ensure the benefits outweigh the risks of repotrectinib for the treatment of patients with locally advanced or metastatic ROS1-positive NSCLC. The management of the risks associated with repotrectinib treatment will be communicated through labeling. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 References

[1] Draft Prescribing Information for repotrectinib as currently edited by the FDA, last updated October 29, 2023.

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