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	216340
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Reviewer Name	Bob Pratt, Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Associate Director for REMS Design and Evaluation	Laura Zendel, PharmD, BCPS

Subject	Evaluation of Need for a REMS
Review Completion Date	December 1, 2022
Established Name	Adagrasib
Trade Name	Krazati
Name of Applicant	Mirati Therapeutics Inc.
Therapeutic Class	Inhibitor of KRAS G12C
Formulation(s)	200 mg tablets
Dosing Regimen	600 mg taken orally twice daily

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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 Krazati (adagrasib) is necessary to ensure the benefits outweigh its risks. Mirati Therapeutics, Inc. submitted a New Drug Application (NDA) 216340 for adagrasib for the proposed indication of treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with KRAS G12C mutation as determined by an FDA approved test and who have received at least one prior systemic therapy. The indication will be approved under accelerated approval based on overall response rate and durability of response. Regular approval for adagrasib will be contingent upon verification and description of clinical benefit in a confirmatory trial. The serious risks associated with adagrasib are gastrointestinal adverse reactions, QTc interval prolongation, hepatotoxicity, and interstitial lung disease/pneumonitis. Adagrasib will be the second KRAS G12C mutation inhibitor for the treatment of NSCLC. The applicant did not submit a proposed REMS or risk management plan with the application.

DRM and the Division of Oncology 2 (DO2) agree that a REMS is not needed to ensure the benefits of adagrasib outweigh its risks. The efficacy of adagrasib is supported by data from a Phase 2 cohort in Study 849-001, in which previously treated patients with NSCLC with KRAS G12C mutations had an overall response rate of 43% with a median duration of response of 8.5 months. The risks of gastrointestinal adverse reactions, QTc interval prolongation, hepatotoxicity, and interstitial lung disease/pneumonitis associated with adagrasib will be described in the Warnings and Precautions of the Prescribing Information. At the time of this review, none of these risks warrant a Boxed Warning. The likely prescribers of adagrasib will be medical oncologists who should have experience in managing the serious risks associated with adagrasib. The review team concluded that the efficacy results are reasonably likely to predict clinical benefit and that adagrasib has an acceptable safety profile when assessed in the context of a life-threatening condition. Overall, the benefit–risk assessment of adagrasib is favorable and supports accelerated approval.

1 Introduction

This review evaluates whether a REMS for the new molecular entity (NME)[a] Krazati (adagrasib) is necessary to ensure the benefits outweigh its risks. Mirati Therapeutics, Inc. submitted a New Drug Application (NDA) 216340 for adagrasib for the proposed indication of treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with KRAS G12C mutation as determined by an FDA approved test and who have received at least one prior systemic therapy. This indication will be approved under accelerated approval based on overall response rate and durability of response. Regular approval for adagrasib will be contingent upon verification and description of clinical benefit in a confirmatory trial. This application is under review in DO2. The Applicant did not submit a proposed REMS or risk management plan with the application.

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

2 Background

2.1 PRODUCT INFORMATION

Rat sarcoma (RAS) proteins, including KRAS, are part of a family of guanosine triphosphatases (GTPases) that are activated in response to the binding of growth factor to regulate intracellular signaling pathways responsible for growth, migration, survival, and differentiation of cells.[1] Compared with wild-type KRAS, which maintains a balance between inactive and activated states, cysteine-12 mutations lock KRAS in a constitutively active state and establish a signal axis of tumor cell proliferation and survival.[2] Adagrasib is an orally available, small molecule inhibitor of KRAS G12C that irreversibly binds the mutant cysteine and locks the mutant KRAS in its inactive state. This prevents downstream signaling without affecting wild-type KRAS protein.[3] Adagrasib is proposed for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with KRAS G12C mutation as determined by an FDA approved test and who have received at least one prior systemic therapy. Adagrasib is supplied as 200 mg tablets. The proposed dosing regimen is 600 mg orally twice daily until disease progression or unacceptable toxicity.[b] Adagrasib is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 216340 relevant to this review:

- 5/20/2020: Fast Track designation granted.
- 6/7/2021: Orphan product designation granted.
- 6/24/2021: Breakthrough Therapy designation granted.
- 12/14/2021: Final submission of NDA 216340 rolling review for the proposed indication of treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with KRAS G12C mutation as determined by an FDA approved test, and who have received at least one prior systemic therapy.
- 5/3/2022: The Mid-Cycle Communication meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Appilcant that there are no major safety concerns identified at this time and there is currently no need for a REMS.
- 10/3/2022: The Late-Cycle meeting was held between the Agency and the Applicant via teleconference. There was no discussion relating to REMS.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Lung cancer is the leading cause of cancer-related deaths worldwide and in the United States. In 2022, an estimated 236,740 new cases of lung cancer will be diagnosed in the U.S. and 130,180 people will die from the disease. The 5-year relative survival rate for patients with regional extension is approximately 33% and with distant-stage disease is approximately 6%.[4]

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

Most lung cancers are classified as either NSCLC (82%) or small cell lung cancer (14%), and approximately half of NSCLC are classified as adenocarcinoma of the lung. It is estimated that 14% of patients with non-small cell lung adenocarcinoma have the KRAS G12C mutation, which is approximately 15,000 cases per year in the U.S.[1,c] Median overall survival (OS) using various second-line chemotherapy regimens for the treatment of NSCLC has varied between approximately 5.7 and 10.5 months.[5,d]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Treatment of patients with lung cancer depends upon the histology, tumor stage, molecular characteristics, and an assessment of the patient's overall medical condition. Available systemic therapy options that are widely used include immunotherapy, cytotoxic chemotherapy, biologics, and targeted agents.

First-line options for the treatment of patients with KRAS G12C-mutated NSCLC include immunotherapy alone or in combination with platinum-based chemotherapy. However, most patients progress on first-line chemo-immunotherapy. Second-line treatment options for this population include pemetrexed or docetaxel monotherapy or docetaxel in combination with ramucirumab, among other treatments. Sotorasib, an inhibitor of KRAS G12C, received accelerated approval in May 2021 for the treatment of patients with advanced NSCLC with a KRAS G12C mutation who have received at least one prior systemic therapy. Sotorasib forms an irreversible, covalent bond with the cysteine of KRAS G12C, locking the protein in an inactive state and blocking KRAS signaling.[6]

4 Benefit Assessment

The efficacy of adagrasib was evaluated in Study 849-001 (NCT03785249), a Phase 2, multicenter, single-arm, open-label expansion cohort study. Patients were required to have locally advanced unresectable or metastatic KRAS G12C-mutated NSCLC and previous treatment with a platinum-based regimen and immune checkpoint inhibitor. The primary efficacy endpoint was overall response rate (ORR) as assessed by an independent central review committee according to the Response Evaluation Criteria in Solid Tumors (RECIST). Secondary endpoints included duration of response (DOR) as well as other endpoints. The patients (N=112) in the treatment cohort (referred to as Cohort A) received adagrasib 600 mg orally twice daily continuously until disease progression, unacceptable adverse events, patient refusal, or death. The treatment cohort had an ORR of 43% (95% C.I., 34% to 53%) with a median DOR of 8.5 months (95% C.I., 6.2 to 13.8).[e,7]

The confirmatory study is an ongoing randomized Phase 3 comparative clinical trial of adagrasib versus docetaxel in adult patients with KRAS G12C mutated, locally advanced or metastatic NSCLC who have

[b] 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.*
[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.*

received at least one prior systemic therapy, to obtain overall survival, progression free survival, overall response rate, and the duration of response.

The draft multidisciplinary review notes that there remains an unmet medical need for patients with KRAS G12C mutated NSCLC who have received at least one prior systemic therapy. This conclusion is based on the observed ORRs, DORs, and overall survival reported for therapies currently used in clinical practice for the treatment of this patient population.

5 Risk Assessment & Safe-Use Conditions

The pooled safety population includes data from 366 patients with NSCLC and other solid tumors who received at least one dose at the 600 mg twice daily dose level. The median duration of treatment in the safety population was 4.9 months (range: 0.03 to 28.7).

5.1 Serious and Severe Adverse Events[f]

Serious adverse events (SAEs) occurred in 177 (48%) patients in the pooled safety population. The most common SAEs reported in patients by System Organ Class (SOC) were Infections and infestations (19%), Respiratory, thoracic, and mediastinal disorders (17%), and Cardiac disorders (10%). The most common SAEs by Preferred Term (PT) were pneumonia (9%), malignant neoplasm progression (6%), dyspnea (5%), acute kidney injury (4%), sepsis (3%), arrhythmia (3%), and hyponatremia (3%).[7]

Severe treatment-emergent adverse events (TEAE) ≥ Grade 3 were reported in a total of 251 (69%) patients. The most common severe adverse events by PT (excluding malignant neoplasm progression and laboratory abnormalities) were pneumonia (10%), fatigue (8%), dyspnea (7%), and hepatotoxicity (8%).[7]

Of the 116 patients who received adagrasib in treatment Cohort A, 20 patients (17%) experienced TEAEs with a fatal outcome within 28 days after the last dose. The clinical safety reviewer noted that the majority of deaths (N=7) were due to disease progression. Fatal adverse events for which adagrasib's involvement could not be ruled out include pneumonia (N=4), respiratory failure (N=2), sudden death (N=2), cardiac failure (N=1), cerebrovascular accident (N=1), mental status change (N=1), pulmonary embolism (N=1), and pulmonary hemorrhage (N=1).[7]

5.2 Adverse Events of Special Interest

5.2.1 Gastrointestinal Adverse Reactions

In the pooled safety population, the most common gastrointestinal adverse events in patients were nausea (70%), diarrhea (69%), and vomiting (57%), which led to dosage interruption or reduction in 29% of patients.[7] Serious gastrointestinal adverse events included intestinal obstruction (N=4) and gastrointestinal bleeding (N=3).[8]

The draft label includes a Warning and Precaution for gastrointestinal adverse reactions that states patients are to be monitored and managed using supportive care, including antidiarrheals, antiemetics, or

[f] 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.*

fluid replacement, as indicated. Prescribers are to withhold, reduce the dose, or permanently discontinue adagrasib based on the severity of the adverse reaction.

5.2.2 QTc Interval Prolongation

In the pooled safety population, 23 (6%) of 366 patients with at least one post-baseline electrocardiogram (ECG) had a QTc maximum on-treatment value > 500 msec, and 41 (11%) patients had an increase from baseline of > 60 msec. The draft multidisciplinary review notes that while no definitive arrhythmias related to QTc prolongation have been observed, cases of sudden death have been observed. Of the two patients who experienced sudden death in Cohort A, a widened QTc interval was observed in one patient approximately six months prior to death, however, no subsequent ECGs were provided for review. The second patient's pre- and post-dose mean QTc intervals were 456 msec and 447 msec, respectively.[7] One patient in a cohort using adagrasib for the treatment of colorectal cancer experienced a fatal cardiac arrest on Day 86 of treatment. The Agency's clinical cardiology consultant considered this event as probably related to treatment because the QTc was prolonged to 500 msec the day before the cardiac arrest.[9]

The draft label includes a Warning and Precaution for QTc interval prolongation that advises prescribers to monitor ECG and electrolytes in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, and in patients who are taking medications that are known to prolong the QT interval. Prescribers are to withhold, reduce the dose, or permanently discontinue adagrasib depending on event severity. Prescribers are to also avoid concomitant use of adagrasib with other products with a known potential to prolong the QTc interval and to avoid use of adagrasib in patients with congenital long QT syndrome and in patients with concurrent QTc prolongation.

5.2.3 Hepatotoxicity

In the pooled safety population, hepatotoxicity occurred in 137 (37%) of 366 patients. Seven percent (7%) of patients developed Grade 3 or greater increased alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels. The median time to first onset of increased ALT/AST was 3 weeks (range: 0.1 to 48). Increased ALT/AST leading to dose interruption or reduction occurred in 11% of patients and discontinuation of treatment in 0.5% of patients. Based upon the review team's analysis, six potential Hy's Law cases were identified and reviewed. Of those, only one case met laboratory criteria for Hy's Law, however, it was in the setting of biliary obstruction from disease progression. Thus, the team concluded no events of drug-induced liver injury met Hy's Law criteria.[7]

The draft label includes a Warning and Precaution for hepatotoxicity that states liver laboratory tests (AST, ALT, alkaline phosphatase and total bilirubin) are to be monitored prior to the start of adagrasib and monthly for 3 months or as clinically indicated, with more frequent testing in patients who develop transaminase elevations. Prescribers are to withhold, reduce the dose, or permanently discontinue adagrasib depending on the severity of the adverse reaction.

5.2.4 Interstitial lung disease/pneumonitis

In the pooled safety population interstitial lung disease (ILD)/pneumonitis occurred in 4.1% (N=15/366) of patients. One and four tenths percent (1.4%) of patients developed Grade 3 or greater ILD/pneumonitis

and one case resulted in a fatal outcome. The median time to onset was 12 weeks (range: 5 to 31 weeks) and adagrasib was discontinued due to ILD/pneumonitis in 3 (0.8%) patients.[7]

The draft label includes a Warning and Precaution for ILD/pneumonitis that states patients are to be monitored for new or worsening respiratory symptoms indicative of ILD/pneumonitis, such as dyspnea, cough, or fever. Prescribers are to withhold adagrasib in patients with suspected ILD/pneumonitis and permanently discontinue the drug if no other potential causes of ILD/pneumonitis are identified.

6 Expected Postmarket Use

Adagrasib will likely be prescribed by medical oncologists who should be familiar with the management of the serious risks associated with the product. As an oral medication, adagrasib will be administered in both the outpatient and inpatient settings.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not submit a proposed REMS or risk management plan with the application.

8 Discussion of Need for a REMS

The review team recommends accelerated approval of adagrasib for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least one prior systemic therapy. Non-small cell lung cancer is a major cause of cancer-related mortality and there remains a need for additional treatment options for patients with KRAS-mutant NSCLC after failure of prior therapy. Adagrasib demonstrated an ORR of 43% (95% C.I., 34% to 53%) with a median DOR of 8.5 months (95% C.I., 6.2 to 13.8).

The serious risks of adagrasib include gastrointestinal adverse reactions, QTc interval prolongation, hepatotoxicity, and interstial lung disease and pneumonitis. These risks will be communicated in the Warnings and Precautions section of the label. At the time of this review, none of these risks warrant a Boxed Warning. The likely prescribers will be medical oncologists who should be familiar with managing the serious risks associated with adagrasib. The review team concluded that the efficacy results are reasonably likely to predict clinical benefit and that adagrasib has an acceptable safety profile when assessed in the context of a life-threatening condition. Information in the Warnings and Precautions and Dosage and Administration sections of the label address the risks adequately. Therefore, at this time, DRM and DO2 have determined a REMS is not necessary to ensure the benefits outweigh the risks of adagrasib.

9 Conclusion & Recommendations

Based on the available data, the benefit-risk profile is favorable and a REMS is not necessary to ensure the benefits of adagrasib outweigh its risks. 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

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ROBERT G PRATT
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LAURA A ZENDEL on behalf of NAOMI S BOSTON
12/01/2022 01:45:55 PM

LAURA A ZENDEL
12/01/2022 01:46:00 PM