# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 213591Orig1s000

# 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 | 213591 |
| PDUFA Goal Date | April 30, 2020 |
| OSE RCM # | 2019-2115 |
| Reviewer Name(s) | Joyce Weaver, Pharm.D. |
| Team Leader | Naomi Boston, Pharm.D. |
| Division Director | Cynthia LaCivita, Pharm.D. |
| Review Completion Date | Draft March 25, 2020 |
| Subject | Evaluation of Need for a REMS |
| Established Name | Capmatinib |
| Trade Name | Tabrecta |
| Name of Applicant | Novartis Pharmaceuticals |
| Therapeutic Class | Kinase inhibitor |
| Formulation(s) | 150 and 200 mg film-coated tablets |
| Dosing Regimen | 400 mg orally twice daily |

Table of Contents

EXECUTIVE SUMMARY ..... 3

1 Introduction ..... 3

2 Background ..... 3

2.1 Product Information ..... 3

2.2 Regulatory History ..... 3

3 Therapeutic Context and Treatment Options ..... 4

3.1 Description of the Medical Condition ..... 4

3.2 Description of Current Treatment Options ..... 4

4 Benefit Assessment ..... 4

5 Risk Assessment & Safe-Use Conditions ..... 5

5.1 Interstitial lung disease/Pneumonitis ..... 5

5.2 Hepatotoxicity ..... 5

5.3 Embryo-fetal Toxicity ..... 5

6 Expected Postmarket Use ..... 6

7 Risk Management Activities Proposed by the Applicant ..... 6

8 Discussion of Need for a REMS ..... 6

9 Conclusion & Recommendations ..... 7

10 Appendices ..... 7

10.1 References ..... 7

# 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 (NME) capmatinib is necessary to ensure the benefits outweigh its risks. Novartis submitted a New Drug Application (NDA) 213591 for capmatinib with the proposed indication for the treatment of patients with locally advanced or metastatic non-cell lung cancer (NSCLC) with a mesachymal-epithelial transition (MET) exon 14 skipping mutation as detected by an FDA-approved test.

Capmatinib has risks of interstitial lung disease, hepatotoxicity, and embryo-fetal toxicity. A boxed warning has not been proposed.

The applicant did not propose a REMS or a risk management program for capmatinib. DRM agrees that a REMS is not needed to ensure the benefits of capmatinib exceeds its risks for the proposed indication.

# 1 Introduction

This review by the DRM evaluates whether a REMS for the NME capmatinib is needed to ensure its benefits outweigh its risks. Novartis submitted a New Drug Application (NDA 213591) for capmatinib with the proposed indication for the treatment of patients with locally advanced or metastatic non-cell lung cancer (NSCLC) with a mesachymal-epithelial transition (MET) exon 14 skipping mutation as detected by an FDA-approved test.

# 2 Background

## 2.1 PRODUCT INFORMATION

Capmatinib, a new molecular entity[a], is to be supplied as 150 mg and 200 mg film-coated tablets. The proposed dose is 400 mg orally twice daily. Treatment continues until disease progression, or the patient experiences intolerable side effects.[b]

## 2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 212578 relevant to this review:

- 3/15/2019: Orphan Drug Designation granted
- 7/22/2019: Pre-NDA meeting; REMS not discussed

[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.*

- 7/29/2019: Breakthrough Therapy Designation granted
- 10/15/2019: Application submitted; request for priority review
- 3/3/2020: Mid-cycle Communication Meeting with applicant canceled because the Agency had no issues to communicate

# 3 Therapeutic Context and Treatment Options

## 3.1 Description of the Medical Condition

The American Cancer Society estimates that in 2020 there will be about 228,820 new cases of lung cancer and 135,720 deaths from the disease.[c,1] Non-small cell lung cancer comprises most (85%) of all lung cancer cases, and MET mutations leading to exon 14 skipping occur in about 5% of the NSCLC cases.[2]

## 3.2 Description of Current Treatment Options

Treatment options include surgery, radiation, and chemotherapy (cisplatin or carboplatin plus docetaxel, gemcitabine, paclitaxel, vinorelbine, or pemetrexed). Patients whose cancer contains certain molecular biomarkers may receive a targeted drug alone or in combination with chemotherapy.[3] Targeted therapies include erlotinib, afatinib, gefitinb, bevacizumab, crizotinib, and ceritinib.[3] Second-line therapy includes atezolizumab, pembrolizumab, nivolumab, ramucirumab.[4]

# 4 Benefit Assessment

The efficacy of capmatinib was examined in an open-label, nonrandomized trial in 97 patients with MET exon 14 skipping mutation metastatic NSCLC.[5] The mean age of patients was 71 years. The patients were mostly white (75%), and most (60%) had never smoked.

The primary efficacy measures in the trial were the overall response rate. A secondary endpoint was duration of response. The overall response rate was 41%, with all responders experiencing a partial response. Sixty-four percent of patients had a duration of response of 6 months or longer.

# 5 Risk Assessment & Safe-Use Conditions

[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.*

The safety database comprises 541 patients. The safety issues included in the draft *Warnings and Precautions* section of the labeling include interstitial lung disease (ILD)/pneumonitis, hepatotoxicity, embryo-fetal toxicity, and photosensitivity.[d]

### 5.1 INTERSTITIAL LUNG DISEASE/PNEUMONITIS

Fifteen patients (2.8%) had ILD/pneumonitis, including six grade 3 cases, and one case that resulted in death.

The draft labeling advises that patients should be evaluated if they experience pulmonary symptoms (e.g., dyspnea, cough, fever). Capmatinib should be discontinued in suspected ILD/pneumonitis.

### 5.2 HEPATOTOXICITY

Elevation of hepatic transaminases occurred in 13% of patients. The elevations occurred within 3 months of beginning therapy with capmatinib. The median time to onset of grade 3 or higher hepatotoxicity was 6.1 weeks (range, 2 to 18 weeks).

The draft labeling advises prescribers to monitor hepatic transaminases before treatment, every 2 weeks for the first 3 months, and then at least monthly thereafter. Should increases in transaminases or bilirubin occur, capmatinib can be held, or, for less severe elevations, the dose of capmatinib can be reduced.

### 5.3 EMBRYO-FETAL TOXICITY

Based on findings from animal studies, it is believed that capmatinib can cause embryo-fetal toxicity. The draft labeling advises that females of reproductive potential should use contraception while receiving capmatinib, and for 7 days after discontinuation. Male patients with female partners of reproductive potential should use (b) (4) while receiving capmatinib, and for 7 days after discontinuation.

## 6 Expected Postmarket Use

Capmatinib would likely be used by patients for the treatment of locally advanced or metastatic NSCLC with a MET exon 14 skipping mutation (the proposed indication). As an oral medication, capmatinib likely would be dispensed by a variety of pharmacy dispensing settings, including retail pharmacies.

[d] 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.*

# 7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose a REMS or other risk mitigation, beyond labeling and routine pharmacovigilance.

# 8 Discussion of Need for a REMS

The clinical reviewers concluded the data support a favorable benefit:risk assessment for capmatinib for the treatment of patients with locally advanced or metastatic non-cell lung cancer (NSCLC) with a mesachymal-epithelial transition (MET) exon 14 skipping mutation as detected by an FDA-approved test. The clinical trial showed a clinically meaningful treatment effect, with an overall response rate of 41%. Sixty-four percent of patients had a duration of response of 6 months or longer.

The clinical reviewer's preliminary findings are that the application is appropriate for accelerated approval and the risks of interstitial lung disease, hepatotoxicity, embryo-fetal toxicity, and photosensitivity will be included in *Warnings and Precautions* (not boxed).[e] The clinical reviewers believe the adverse events are manageable with dose reduction, interruption, or discontinuance, and the events are appropriately handled with labeling alone.

This reviewer recommends that, should capmatinib be approved, a REMS is not needed to ensure its benefits outweigh its risks. Interstitial lung disease, hepatotoxicity, and embryo-fetal toxicity can be adequately described in the labeling. None of the risks of capmatinib warrants a boxed warning. DRM agrees with this analysis, healthcare providers who will prescribe and administer capmatinib are expected to be able to manage the capmatinib -emergent adverse events without additional risk mitigation measures beyond labeling..

# 9 Conclusion & Recommendations

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

[e] The clinical review was ongoing at the time of this review.

[1] https://www.ncbi.nlm.nih.gov/pubmed/31912902. Accessed February 28, 2020.

[2] Heist R et al. MET exon 14 skipping in non-small cell lung cancer. Oncologist. 2016 Apr; 21(4): 481–486.

[3] https://www.lungcancer.org/find_information/publications/163-lung_cancer_101/269-non_small_cell_lung_cancer_treatment. Accessed March 5 2020.

[4] Mathieu L, clinical reviewer. Mid-cycle meeting February 12, 2020.

[5] Clinical Trials Register: NCT# 02414139

---

**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

---

/s/

---

JOYCE P WEAVER
03/30/2020 08:32:54 AM

CYNTHIA L LACIVITA on behalf of NAOMI S BOSTON
03/30/2020 10:53:07 AM

CYNTHIA L LACIVITA
03/30/2020 11:01:00 AM