CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213721Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
<table>
<thead>
<tr>
<th>Application Type</th>
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<tr>
<td>Reviewer Name(s)</td>
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<td>Review Completion Date</td>
<td>September 2, 2020</td>
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<tr>
<td>Subject</td>
<td>Evaluation of Need for a REMS</td>
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<tr>
<td>Established Name</td>
<td>Gavreto</td>
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<td>Trade Name</td>
<td>Pralsetinib</td>
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<tr>
<td>Name of Applicant</td>
<td>Blueprint Medicines</td>
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<tr>
<td>Therapeutic Class</td>
<td>Kinase inhibitor</td>
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<tr>
<td>Formulation(s)</td>
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<tr>
<td>Dosing Regimen</td>
<td>400 mg orally once daily</td>
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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 (NME) pralsetinib is necessary to ensure the benefits outweigh its risks. Blueprint Medicines submitted a New Drug Application (NDA) 213721 for pralsetinib with the proposed indication for the treatment of adult patients with metastatic rearranged during transfection (RET) fusion positive non-cell lung cancer (NSCLC) as detected by an FDA-approved test.

Pralsetinib has risks of interstitial lung disease/pneumonitis, hypertension, hepatotoxicity, hemorrhagic events, risk of impaired wound healing, and embryo-fetal toxicity. A boxed warning has not been proposed.

The proposed label does not include a Boxed Warning, and the risks associated with pralsetinib will be included under Warnings and Precautions. DRM and the Division of Oncology Products 2 (DOP 2) agree that a REMS is not needed to ensure the benefits of pralsetinib outweigh its risks.

1 Introduction

This review by the DRM evaluates whether a REMS for the NME pralsetinib is needed to ensure its benefits outweigh its risks. Blueprint Medicines submitted a New Drug Application (NDA 213591) for pralsetinib with the proposed indication for the treatment of patients with rearranged during transfection (RET)-positive locally advanced or metastatic non-cell lung cancer (NSCLC) as detected by an FDA-approved test. This application is being reviewed in the Division of Oncology Products 2 (DOP 2).

2 Background

2.1 PRODUCT INFORMATION

Pralsetinib is a kinase inhibitor indicated for the treatment of adult patients with metastatic rearranged during transfection (RET fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test.
Pralsetinib, a new molecular entity\textsuperscript{a}, is to be supplied as 100mg capsule. The proposed dose is 400 mg orally once daily. Treatment continues until disease progression, or until the patient experiences intolerable side effects.\textsuperscript{b}

Pralsetinib is currently not approved in any other jurisdictions.

### 2.2 Regulatory History

The following is a summary of the regulatory history for NDA 213721 relevant to this review:

- 4/11/2018: Orphan Drug Designation granted
- 10/30/2019: Breakthrough Therapy Designation granted
- 3/23/2020: Application submitted; request for priority review
- 6/23/2020: Late-Cycle Meeting with Applicant

### 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.\textsuperscript{c,1} Non-small cell lung cancer comprises most (85\%) of all lung cancer cases, and RET mutations occur in 2\% of NSCLC cases.\textsuperscript{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.\textsuperscript{3} Targeted therapies include erlotinib, afatinib, gefitinib, crizotinib, and ceritinib.\textsuperscript{3} Adjunctive therapies include atezolizumab, pembrolizumab, nivolumab.\textsuperscript{4}

### 4 Benefit Assessment

\textsuperscript{a} Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.

\textsuperscript{b} Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.

\textsuperscript{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.
A summary of efficacy is included in this section, for full details please see the Assessment Aid, which had not been finalized at the time of our review.

The efficacy of pralsetinib was evaluated in patients with RET fusion positive metastatic NSCLC in a multicenter, non-randomized, open-label trial (ARROW, NCT03037385). This trial included 87 patients with RET fusion-positive NSCLC with measurable disease who were previously treated with platinum chemotherapy. The median age was 60 years (range: 28 to 85); 49% were female, 53% were White, 35% were Asian and 6% were Hispanic/Latino.

The primary efficacy measures in the trial were the overall response rate and duration of response.

The clinical reviewer concluded that the overall response rate in the RET fusion-positive NSCLC population was 57% (95% CI: 46%, 68%; n=87) in patients with prior platinum treatment and 70% (95% CI: 60 60%, 86%; n=27) in treatment-naïve patients as shown in Table 1.

Table 1: Efficacy Results for ARROW (treatment naïve metastatic RET fusion Positive NSCLC)

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>GAVRETO (N=27)</th>
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<tr>
<td>Overall Response Rate (ORR)(^{a}) (95% CI)</td>
<td>70 (50, 86)</td>
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<tr>
<td>Complete Response, %</td>
<td>11</td>
</tr>
<tr>
<td>Partial Response, %</td>
<td>59</td>
</tr>
<tr>
<td>Duration of Response (DOR) (N=19)</td>
<td></td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>9.0 (6.3, NE)</td>
</tr>
<tr>
<td>Patients with DOR ≥ 6-months(^{b}), %</td>
<td>58</td>
</tr>
</tbody>
</table>

5 Risk Assessment & Safe-Use Conditions

The pooled safety analysis comprises 404 patients. The safety issues included in the draft Warnings and Precautions section of the labeling include interstitial lung disease (ILD)/pneumonitis, hypertension, hepatotoxicity, hemorrhagic events, risk of impaired wound healing and embryo-fetal toxicity. A summary of the safety issues is included in this section, for full details please see the Assessment Aid, which had not been finalized at the time of our review.
5.1 INTERSTITIAL LUNG DISEASE/PNEUMONITIS

The draft labeling advises that patients should be evaluated if they experience symptoms indicative of pneumonitis (e.g., dyspnea, cough, fever).

5.2 EMBRYO-FETAL TOXICITY

Based on findings from animal studies, it is believed that pralsetinib can cause embryo-fetal toxicity. A comprehensive nonclinical toxicology program assessed the potential of embryofetal toxicity. Key study findings from these evaluations concluded that Pralsetinib induced 100% embryo-fetal mortality due to post-implantation loss (early resorptions) at dose levels ≥20 mg/kg (approximately 1.5 times the exposure based on AUC at the human dose of 400 mg) accompanied by reduced gravid uterine weight. In addition, Pralsetinib was teratogenic at doses ≥5 mg/kg (approximately 0.2 times the exposure based on AUC at the human dose of 400 mg), producing visceral and skeletal malformations and variations. The draft labeling advises females of reproductive potential of the potential risk to a fetus. As prasetinib has been identified as a CYP3A inducer, which may compromise the efficacy of hormonal contraception, the label will advise females of reproductive potential to use effective non-hormonal contraception during treatment and for 2 weeks after the final dose. Males of reproductive potential will be advised to use effective contraception while receiving pralsetinib and for one week after the final dose.

5.3 HEPATOTOXICITY

Serious hepatic adverse reactions occurred in 2.1% of patients treated for pralsetinib. Increased AST occurred in 69% of patients, including Grade 3 or 4 in 5.4% and increased ALT occurred in 46% of patients, including Grade 3 or 4 in 6% of patients. The median time to first onset for increased AST was 15 days (range: 5 days to 1.5 years) and increased ALT was 22 days (range: 7 days to 1.7 years).

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 and as clinically indicated. The labeling indicates to withhold, reduce dose, or permanently discontinue pralsetinib based on the severity of hepatotoxic events.
6 Expected Postmarket Use

Pralsetinib would likely be used by patients with rearranged during transfection (RET)-positive locally advanced or metastatic NSCLC (the proposed indication). As an oral medication, pralsetinib would likely be dispensed by a variety of pharmacy dispensing settings, including retail pharmacies.

Pralsetinib will likely be prescribed by oncologists who are familiar with similar adverse events associated with treatment of adult patients with metastatic rearranged during transfection (RET fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test.

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 pralsetinib for the treatment of adult patients with metastatic rearranged during transfection (RET) fusion positive non-cell lung cancer (NSCLC) as detected by an FDA-approved test. The clinical trial showed a clinically meaningful treatment effect, with an overall response rate of durable tumor responses, with 80% of patients having tumor responses lasting 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/pneumonitis, hypertension, hepatotoxicity, hemorrhagic events, risk of impaired wound healing and embryo-fetal toxicity, and will be included in Warnings and Precautions (not boxed). 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 pralsetinib 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 pralsetinib warrant a boxed warning. Healthcare providers who will prescribe pralsetinib are expected to be able to

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d The clinical review was ongoing at the time of this review.
manage the pralsetinib-emergent adverse events without additional risk mitigation measures beyond labeling.

9 Conclusion & Recommendations

The DOP2 and DRM agree that a REMS is not necessary to ensure the benefits of pralsetinib 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


4 Kim J, Clinical Reviewer. Praseltinib Assessment Aid.

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/s/

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