

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761210Orig1s000

**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	BLA
Application Number	761210
PDUFA Goal Date	May 21, 2021
OSE RCM #	2020-2486
Reviewer Name(s)	Joyce Weaver, Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	April 23, 2021
Subject	Evaluation of Need for a REMS
Established Name	Amivantamab
Trade Name	Rybrevant
Name of Applicant	Janssen
Therapeutic Class	EGFR-MET bispecific antibody
Formulation(s)	Solution for intravenous infusion: 50 mg/mL
Dosing Regimen	1050 mg intravenously once weekly X 4 weeks, then every 2 weeks (1400 mg for patients > 80 kg)

Table of Contents

EGFR-MET bispecific antibody	1
EXECUTIVE SUMMARY	3
1 Introduction.....	3
2 Background.....	3
2.1 Product Information.....	3
2.2 Regulatory History.....	4
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 Infusion-Related Reactions	5
5.2 Interstitial Lung Disease/Pneumonitis	6
5.3 Dermatologic Adverse Reactions.....	6
5.4 Ocular Toxicities.....	6
5.5 Embryo-fetal Toxicity	6
6 Expected Postmarket Use	7
7 Risk Management Activities Proposed by the Applicant.....	7
8 Discussion of Need for a REMS.....	7
9 Conclusion & Recommendations.....	7
10 Appendices	8
10.1 References.....	8

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) amivantamab is necessary to ensure the benefits outweigh its risks. Janssen submitted a Biologics License Application (BLA) 761210 for amivantamab with the proposed indication for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (*EGFR*) exon 20 insertion mutation whose disease has progressed on or after platinum-based chemotherapy^a.

Amivantamab has risks of infusion-related reactions, interstitial lung disease, skin and nail reactions, eye disorders, and embryo-fetal toxicity. A boxed warning is not proposed for any risk.

The applicant did not propose a REMS or a risk management program for amivantamab. DRM agrees that a REMS is not needed to ensure the benefits of amivantamab outweigh its risks for the proposed indication. The risks of infusion-related reactions, interstitial lung disease/pneumonitis, dermatologic adverse reactions, ocular disorders, and embryo-fetal toxicity are adequately described in the *Warnings and Precautions* section of the labeling. A boxed warning is not proposed for any risk. Healthcare providers who will prescribe and administer amivantamab are expected to be able to manage the amivantamab-emergent adverse events without additional risk mitigation measures beyond labeling.

1 Introduction

This review by the DRM evaluates whether a REMS for the NME amivantamab is needed to ensure its benefits outweigh its risks. Janssen submitted BLA 761210 for amivantamab with the proposed indication for the treatment of patients with metastatic NSCLC with *EGFR* exon 20 insertion mutation whose disease has progressed on or after platinum-based chemotherapy.

2 Background

2.1 PRODUCT INFORMATION

Amivantamab, a new molecular entity^b, is to be supplied as 50 mg/mL solution for further dilution and infusion. For patients less than 80 kg of body weight, the proposed dose is 1050 mg

^a The division has changed the indication statement to, “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 mutation, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy “

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

once weekly for 4 weeks, followed by once every 2 weeks thereafter. The first dose is split into two infusions (350 mg and 700 mg) on Days 1 and 2. For patients weighing 80 kg or more, the dose is 1400 mg administered according to the same schedule, with the first dose split into 350 mg on Day 1 and 1050 mg on Day 2. Treatment continues until disease progression or unacceptable toxicity.^c Amivantamab is not approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761210 relevant to this review:

- 3/9/2020: Breakthrough Therapy Designation granted for indication.
- 11/4/2020: Pre-BLA meeting; REMS not discussed (DRM did not participate in the meeting)
- 11/24/2020: BLA submitted
- 2/24/2021: Mid-cycle meeting held

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

The American Cancer Society estimates that in 2021 there will be about 236,000 new cases of lung cancer and 132,000 deaths from the disease.^{d,1} Non-small cell lung cancer comprises most (85%) of all lung cancer cases. *EGFR* mutations occur in 10–20% of Caucasian patients and at least 50% of Asian NSCLC patients². *EGFR* exon 20 mutations represent about 4% of *EGFR* mutations³.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

No treatment has been approved to treat NSCLC with *EGFR* exon 20 mutation. Treatment options for patients include platinum-based chemotherapy, nivolumab, ipilimumab, ramucirumab + docetaxel.⁴

4 Benefit Assessment

^c Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment 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.*

The efficacy of amivantamab was evaluated in a multicenter, open-label, multicohort study⁵. The study included 81 patients with locally advanced or metastatic NSCLC with EGFR Exon 20 insertion mutation whose disease had progressed with platinum-based chemotherapy. The median age of the patients was 62 years (range, 42 to 84). Most (59%) were female and most (74%) weighed <80 kg. Forty-nine percent were Asian and 37% were Caucasian.

Patients received 1050 mg amivantamab (patients weighing < 80 kg) or 1400 mg (patients weighing ≥80 kg) once weekly for 4 weeks, then every 2 weeks thereafter until disease progression or unacceptable toxicity.

Efficacy was measured by overall response rate and duration of response. The overall response was 40% (95% confidence interval, 29%, 51%). The duration of response was 11.1 months (6.9, NE).

5 Risk Assessment & Safe-Use Conditions

The safety database for amivantamab comprises data from 302 patients, 129 of whom received amivantamab for the stated indication. Among the 302 patients who received amivantamab, 36% were exposed for 6 months or longer and 12% were exposed for greater than one year.

Overall, the most frequently reported adverse events were rash (occurred in 78% of patients), infusion reactions (64%), paronychia (50%), nausea (36%), fatigue (33%), stomatitis (26%), peripheral edema (25%), and constipation (23%). Discontinuation of amivantamab due to an adverse reaction occurred in 11% of patients. Adverse reactions resulted in dose interruptions in 76% of patients and resulted in dose reductions in 15% of patients.

The safety issues in the draft *Warnings and Precautions* section of the labeling include risks of infusion-related reactions, interstitial lung disease/pneumonitis, dermatologic adverse reactions, ocular disorders, and embryo-fetal toxicity. A boxed warning has not been proposed for any risk.^e

5.1 INFUSION-RELATED REACTIONS

Amivantamab can cause infusion-related reactions. Most infusion reactions (55%) were Grade 2 reactions. Ninety-three percent occurred with the first infusion. Grade 3 or 4 reactions represented less than 2% of the reactions.

The draft labeling advises healthcare providers to premedicate patients receiving amivantamab with antihistamines, antipyretics, and glucocorticoids, and to monitor patients during

^e 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.*

administration for infusion reactions. Depending on the severity of an infusion reaction, the infusion can be slowed, interrupted, or discontinued.

5.2 INTERSTITIAL LUNG DISEASE/PNEUMONITIS

Amivantamab can cause serious interstitial lung disease/pneumonitis. Interstitial lung disease/pneumonitis occurred in 3.3% of patients, and Grade 3 reactions occurred in 0.7% of patients.

The draft labeling advises healthcare providers to monitor patients clinically for pulmonary signs and symptoms. Amivantamab should be withheld for suspected interstitial lung disease/pneumonitis and stopped permanently if interstitial lung disease/pneumonitis is confirmed.

5.3 DERMATOLOGIC ADVERSE REACTIONS

Amivantamab can cause serious dermatologic reactions. Dermatologic reactions occurred in most patients receiving amivantamab. Grade 3 rash occurred in 3% of patients. One patient experienced toxic epidermal necrolysis (TEN). The median time to onset of rash was 14 days. Rash leading to dose reduction occurred in (b) (4)% of patients, and to discontinuation in 0.7% of patients.

The draft labeling advises HCPs to institute topical steroids and, if needed, antibiotics, for rash. For rash not improving within 2 weeks, the labeling advises HCPs to refer patients to a dermatologist, and withhold, reduce, or discontinue amivantamab. The draft labeling also advises that patients should limit sun exposure during and for 2 months after treatment with amivantamab.

5.4 OCULAR TOXICITIES

Amivantamab can cause ocular toxicities including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, periocular edema, and uveitis. Keratitis occurred in (b) (4)% of patients, and uveitis occurred in 0.3% of patients. The draft labeling advises healthcare providers to refer patients to an ophthalmologist for worsening eye symptoms. Depending on the severity of the reaction, amivantamab can be withheld, the dose can be reduced, or amivantamab can be discontinued.

5.5 EMBRYO-FETAL TOXICITY

Based on the mechanism of action and findings from animal models, it is believed that amivantamab can cause embryo-fetal toxicity. Based on findings with other EGFR inhibitors to animals, it is believed that amivantamab can cause impairment of embryo-fetal development, and embryo loss. The draft labeling advises that female patients of reproductive potential should use effective contraceptive during treatment with amivantamab and for 3 months after the final dose.

6 Expected Postmarket Use

Amivantamab would likely be used by hospitals and oncology infusion centers with the experience and equipment to respond to infusion-related reactions.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose a REMS or other risk mitigation measures.

8 Discussion of Need for a REMS

The clinical team has concluded the data support a favorable benefit:risk assessment for amivantamab 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 mutation, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.” Study data submitted showed an overall response rate of 40% (95% confidence interval, 29%, 51%). The duration of response was 11.1 months (6.9, NE).

The clinical team’s preliminary findings are that the application is appropriate for approval and the risks of infusion-related reactions, interstitial lung disease/pneumonitis, dermatologic adverse reactions, ocular disorders, and embryo-fetal toxicity will be included in *Warnings and Precautions*. None of the risks warrants a boxed warning.^f 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 amivantamab be approved, a REMS is not needed to ensure its benefits outweigh its risks. The risks can be adequately described in the labeling. Amivantamab will most likely be prescribed by oncologists and used in oncology infusion centers and hospitals. Healthcare providers who will prescribe and administer amivantamab are expected to be able to manage the amivantamab-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 amivantamab outweigh its risks. At the time of this review, evaluation of safety information and labeling was

^f The clinical review was ongoing at the time of this review.

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

¹ <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf>. Accessed April 16, 2021.

² <https://www.sciencedirect.com/science/article/pii/S1044579X19303025#bbib0005>. Accessed April 16, 2021.

³ <https://www.sciencedirect.com/science/article/pii/S1470204511701292?via%3Dihub#bbib1>. Accessed April 16, 2021.

⁴ <https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq#link/485162>. Accessed April 16, 2021.

⁵ <https://Clinicaltrials.gov>. NCT02609776. Accessed April 19, 2021.

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
04/23/2021 11:46:05 AM

NAOMI S BOSTON
04/23/2021 11:58:33 AM

DORIS A AUTH
04/23/2021 12:40:29 PM