RYBREVANT® (amivantamab-vmjw) injection, for intravenous use

Indications and Usage (1) 03/2024
Doseage and Administration (2) 03/2024
Warnings and Precautions (5) 03/2024

**INDICATIONS AND USAGE**

RYBREVANT is a bispecific EGF receptor-directed and MET receptor-directed antibody indicated:

- in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test. (1, 2, 2)
- as a single agent for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy. (1, 2, 2)

**DOSAGE AND ADMINISTRATION**

- The recommended dosage of RYBREVANT is based on baseline body weight and administered as an intravenous infusion after dilution. (2.3, 2.5, 2.6, 2.7)
- Administer premedications as recommended. (2.4)
- Administer via a peripheral line on Week 1 and Week 2. (2.7)
- Administer RYBREVANT in combination with chemotherapy weekly for 4 weeks, with the initial dose as a split infusion in Week 1 on Day 1 and Day 2, then administer every 3 weeks starting at Week 7. (2.3)
- Administer RYBREVANT as a single agent weekly for 4 weeks, with the initial dose as a split infusion in Week 1 on Day 1 and Day 2, then administer every 2 weeks starting at Week 5. (2.4)
- Administer diluted RYBREVANT intravenously according to the infusion rates in Tables 7 and 8. (2.8)

<table>
<thead>
<tr>
<th>Body Weight (at Baseline)</th>
<th>Dosage</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>RYBREVANT in Combination with Carboplatin and Pemetrexed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 80 kg</td>
<td>Weeks 1-4</td>
<td>1400 mg</td>
</tr>
<tr>
<td></td>
<td>Week 7 onwards</td>
<td>1750 mg</td>
</tr>
<tr>
<td>Greater than or equal to 80 kgs</td>
<td>Weeks 1-4</td>
<td>1750 mg</td>
</tr>
<tr>
<td></td>
<td>Week 7 onwards</td>
<td>2100 mg</td>
</tr>
<tr>
<td>RYBREVANT as a Single Agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 80 kg</td>
<td>Weeks 1-5</td>
<td>1050 mg</td>
</tr>
<tr>
<td></td>
<td>Week 7 onwards</td>
<td>1400 mg</td>
</tr>
<tr>
<td>Greater than or equal to 80 kg</td>
<td>Weeks 1-5</td>
<td>1400 mg</td>
</tr>
</tbody>
</table>

**WARNINGS AND PRECAUTIONS**

- Infusion-Related Reactions (IRR): Interrupt infusion at the first sign of IRRs. Reduce infusion rate or permanently discontinue RYBREVANT based on severity. (2.5, 5.1)
- Interstitial Lung Disease (ILD)/Pneumonitis: Monitor for new or worsening symptoms indicative of ILD. Immediately withhold RYBREVANT in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed. (2.5, 5.2)
- Dermatologic Adverse Reactions: May cause rash including acniform dermatitis and toxic epidermal necrolysis. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity. (2.5, 5.3)
- Ocular Toxicity: Promptly refer patients with worsening eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity. (2.5, 5.4)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception. (5.5, 8.1, 8.3)

**ADVERSE REACTIONS**

- RYBREVANT in Combination with Carboplatin and Pemetrexed
  - The most common adverse reactions (≥20%) were rash, nail toxicity, stomatitis, infusion-related reaction, fatigue, edema, constipation, decreased appetite, nausea, COVID-19, diarrhea, and vomiting. (6.1)
  - The most common Grade 3 or 4 laboratory abnormalities (≥2%) were decreased albumin, increased alanine aminotransferase, increased gamma-glutamyl transferase, decreased sodium, decreased potassium, decreased magnesium, and decreases in white blood cells, hemoglobin, neutrophils, platelets, and lymphocytes. (6.1)

- RYBREVANT as a Single Agent
  - The most common adverse reactions (≥20%) were rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting. (6.1)
  - The most common Grade 3 or 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased albumin, decreased phosphate, decreased potassium, increased alkaline phosphatase, increased glucose, increased gamma-glutamyl transferase, and decreased sodium. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**USE IN SPECIFIC POPULATIONS**

- Pregnancy: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2024
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 First-Line Treatment of NSCLC with EGFR Exon 20 Insertion Mutations

RYBREVA NT is indicated in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test [see Dosage and Administration (2.2)].

1.2 Previously Treated NSCLC with EGFR Exon 20 Insertion Mutations

RYBREVA NT is indicated as a single agent for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test [see Dosage and Administration (2.2)], whose disease has progressed on or after platinum-based chemotherapy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage Information

• Administer premedications before each RYBREVA NT infusion as recommended [see Dosage and Administration (2.5)].

• Administer diluted RYBREVA NT intravenously according to the infusion rates in Tables 7 and 8, with the initial dose as a split infusion on Week 1 and Day 1 and Day 2 [see Dosage and Administration (2.8)].

• Administer RYBREVA NT via peripheral line for Week 1 Day 1 and 2 and Week 2 to reduce the risk of infusion-related reactions [see Dosage and Administration (2.8)].

• When administering RYBREVA NT in combination with carboplatin and pemetrexed, infuse pemetrexed first, carboplatin second, and RYBREVA NT last [see Dosage and Administration (2.8)].

2.2 Patient Selection

Select patients for treatment with RYBREVA NT based on the presence of EGFR exon 20 insertion mutations in tumor or plasma specimens [see Clinical Studies (14)]. If no mutation is detected in a plasma specimen, test tumor tissue. Information on FDA-approved tests is available at: http://www.fda.gov/CompanionDiagnostics.

2.3 Recommended Dosage of RYBREVA NT for First-Line Treatment of NSCLC with EGFR Exon 20 Insertion Mutations (RYBREVA NT in Combination with Carboplatin and Pemetrexed)

The recommended dosages of RYBREVA NT, administered in combination with carboplatin and pemetrexed, based on baseline body weight are provided in Table 1.

Table 1: Recommended Dosage for RYBREVA NT in Combination with Carboplatin and Pemetrexed

<table>
<thead>
<tr>
<th>Body weight at Baselinea</th>
<th>Recommended Dose</th>
<th>Dosing Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 80 kg</td>
<td>1400 mg</td>
<td>Weekly (total of 4 doses) from Weeks 1 to 4&lt;br&gt;• Week 1 - split infusion on Day 1 and Day 2&lt;br&gt;• Weeks 2 to 4 - infusion on Day 1&lt;br&gt;• Weeks 5 and 6 - no dose&lt;br&gt;1750 mg</td>
</tr>
<tr>
<td>Greater than or equal to 80 kg</td>
<td>1750 mg</td>
<td>Weekly (total of 4 doses) for Weeks 1 to 4&lt;br&gt;• Week 1 - split infusion on Day 1 and Day 2&lt;br&gt;• Weeks 2 to 4 - infusion on Day 1&lt;br&gt;• Weeks 5 and 6 - no dose&lt;br&gt;2100 mg</td>
</tr>
</tbody>
</table>

a Dose adjustments not required for subsequent body weight changes.

2.4 Recommended Dosage of RYBREVA NT for Patients with Previously Treated NSCLC with EGFR Exon 20 Insertion Mutations (RYBREVA NT as a Single Agent)

The recommended dosages of RYBREVA NT as a single agent, based on baseline body weight, are provided in Table 3.

Table 3: Recommended Dosage Schedule for RYBREVA NT as a Single Agent

<table>
<thead>
<tr>
<th>Body weight at Baselinea</th>
<th>Recommended Dose</th>
<th>Dosing Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 80 kg</td>
<td>1050 mg</td>
<td>Weekly (total of 5 doses) from Weeks 1 to 5&lt;br&gt;• Week 1 - split infusion on Day 1 and Day 2&lt;br&gt;• Weeks 2 to 5 - infusion on Day 1&lt;br&gt;• Week 6 – no dose</td>
</tr>
<tr>
<td>Greater than or equal to 80 kg</td>
<td>1400 mg</td>
<td>Weekly (total of 5 doses) from Weeks 1 to 5&lt;br&gt;• Week 1 - split infusion on Day 1 and Day 2&lt;br&gt;• Weeks 2 to 5 - infusion on Day 1&lt;br&gt;• Week 6 – no dose</td>
</tr>
</tbody>
</table>

a Dose adjustments not required for subsequent body weight changes.

Administer RYBREVA NT until disease progression or unacceptable toxicity.

2.5 Recommended Premedications

Prior to the initial infusion of RYBREVA NT (Week 1, Day 1 and 2), administer premedication as described in Table 4 to reduce the risk of infusion-related reactions [see Warnings and Precautions (5.1)].

Glucocorticoid administration is required for Week 1, Day 1 and 2 dose only and upon re-initiation after prolonged dose interruptions, then as necessary for subsequent infusions (see Table 4). Administer both antihistamine and anti-pyretic prior to all infusions.
RYBREVENT® (amivantamab-vmjw) injection

Table 4: Premedications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Route of Administration</th>
<th>Dosing Window Prior to RYBREVENT Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamine*</td>
<td>Diphenhydramine (25 to 50 mg) or equivalent</td>
<td>Oral or Intravenous</td>
<td>30 to 60 minutes</td>
</tr>
<tr>
<td>Antipyretic*</td>
<td>Acetaminophen (650 to 1,000 mg)</td>
<td>Intravenous or Oral</td>
<td>15 to 30 minutes</td>
</tr>
<tr>
<td>Glucocorticoid†</td>
<td>Dexamethasone (20 mg) or equivalent</td>
<td>Intravenous or Oral</td>
<td>45 to 60 minutes</td>
</tr>
<tr>
<td>Glucocorticoid†</td>
<td>Dexamethasone (10 mg) or equivalent</td>
<td>Intravenous or Oral</td>
<td>45 to 60 minutes</td>
</tr>
</tbody>
</table>

* Required at all doses.  
† Required at initial dose (Week 1 Day 1)  
‡ Required at second dose (Week 1 Day 2); optional for subsequent doses.

2.6 Dosage Modifications for Adverse Reactions

The recommended dose reductions for adverse reactions for RYBREVENT are listed in Table 5.

Table 5: Dose Reductions for Adverse Reactions for RYBREVENT

<table>
<thead>
<tr>
<th>Dose*</th>
<th>1st Dose Reduction</th>
<th>2nd Dose Reduction</th>
<th>3rd Dose Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1050 mg</td>
<td>700 mg</td>
<td>350 mg</td>
<td>Discontinue RYBREVENT</td>
</tr>
<tr>
<td>1400 mg</td>
<td>1050 mg</td>
<td>700 mg</td>
<td></td>
</tr>
<tr>
<td>1750 mg</td>
<td>1400 mg</td>
<td>1050 mg</td>
<td></td>
</tr>
<tr>
<td>2100 mg</td>
<td>1750 mg</td>
<td>1400 mg</td>
<td></td>
</tr>
</tbody>
</table>

* Dose at which the adverse reaction occurred

The recommended dosages and management for adverse reactions for RYBREVENT are provided in Table 6.

Table 6: Recommended Dosage Modifications and Management for Adverse Reactions for RYBREVENT

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Dosage Modifications</th>
</tr>
</thead>
</table>
| Infusion-related reactions (IRR)      | Grade 1 to 2 | • Interrupt RYBREVENT infusion if IRR is suspected and monitor patient until reaction symptoms resolve.  
|                                       |          | • Resume the infusion at 50% of the infusion rate at which the reaction occurred.  
|                                       |          | • If there are no additional symptoms after 30 minutes, the infusion rate may be escalated (see Tables 7 and 8).  
|                                       |          | • Include corticosteroid with premedications for subsequent dose (see Table 4). |
| Interstitial Lung Disease (ILD)/pneumonitis | Grade 3 | • Interrupt RYBREVENT infusion and administer supportive care medications. Continuously monitor patient until reaction symptoms resolve.  
|                                       |          | • Resume the infusion at 50% of the infusion rate at which the reaction occurred.  
|                                       |          | • If there are no additional symptoms after 30 minutes, the infusion rate may be escalated (see Tables 7 and 8).  
|                                       |          | • Include corticosteroid with premedications for subsequent dose (see Table 4). |
|                                       | Any Grade | • Withhold RYBREVENT if ILD/pneumonitis is suspected.  
|                                       |          | • Permanently discontinue RYBREVENT if ILD/pneumonitis is confirmed. |

2.7 Preparation

Dilute and prepare RYBREVENT for intravenous infusion before administration.  
- Check that the RYBREVENT solution is colorless to pale yellow. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if discolored or visible particles are present.  
- Determine the dose required of RYBREVENT based on patient’s baseline weight [see Dosage and Administration (2.3)]. Each vial of RYBREVENT contains 350 mg of amivantamab-vmjw.  
- Withdraw and then discard a volume of either 5% dextrose solution or 0.9% sodium chloride solution from the 250 mL infusion bag equal to the volume of RYBREVENT to be added (i.e., discard 7 mL diluent from the infusion bag for each RYBREVENT vial). Only use infusion bags made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE), or polyolefin blend (PP+PE).  
- Withdraw 7 mL of RYBREVENT from each vial and add it to the infusion bag. The final volume in the infusion bag should be 250 mL. Discard any unused portion left in the vial.  
- Gently invert the bag to mix the solution. Do not shake.  
- Diluted solutions should be administered within 10 hours (including infusion time) at room temperature 59°F to 77°F (15°C to 25°C).

2.8 Administration

- Administer the diluted RYBREVENT solution [see Dosage and Administration (2.7)] by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.2 micrometer).
RYBREVANT® (amivantamab-vmjw) injection

- Administration sets must be made of either polyurethane (PU), polybutadiene (PBD), PVC, PP, or PE.
- The administration set with filter, must be primed with either 5% dextrose solution or 0.9% sodium chloride solution prior to the initiation of each RYBREVANT infusion.
- Do not infuse RYBREVANT concomitantly in the same intravenous line with other agents.

**RYBREVANT in Combination with Carboplatin and Pemetrexed**

- Administer RYBREVANT in combination with carboplatin and pemetrexed infusions every 3 weeks intravenously according to the infusion rates in Table 7.
- Administer RYBREVANT via a peripheral line on Week 1 and Week 2 given the high incidence of infusion-related reactions during initial treatment (see Warnings and Precautions (5.1)).
- RYBREVANT may be administered via central line for subsequent weeks.
- For the initial infusion, prepare RYBREVANT as close to administration time as possible to allow for the possibility of extended infusion time in the event of an infusion related reaction.
- Administer the pemetrexed infusion first, carboplatin infusion second, and the RYBREVANT infusion last.

**Table 7: Infusion Rates of RYBREVANT for First-line Treatment of NSCLC with Exon 20 Insertion Mutations (RYBREVANT in Combination with Carboplatin and Pemetrexed)**

<table>
<thead>
<tr>
<th>Week</th>
<th>Dose (per 250 mL bag)</th>
<th>Initial Infusion Rate (mL/hr)</th>
<th>Subsequent Infusion Rate† (mL/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1 (split dose infusion)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 1 Day 1</td>
<td>350 mg</td>
<td>50</td>
<td>75</td>
</tr>
<tr>
<td>Week 1 Day 2</td>
<td>1050 mg</td>
<td>33</td>
<td>50</td>
</tr>
<tr>
<td>Week 2</td>
<td>1400 mg</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td>1400 mg</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>1400 mg</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>Weeks 5 and 6</td>
<td></td>
<td>No dose</td>
<td></td>
</tr>
<tr>
<td>Week 7 and every 3 weeks thereafter</td>
<td>1750 mg</td>
<td></td>
<td>125</td>
</tr>
</tbody>
</table>

1 In the absence of infusion-related reactions, increase the initial infusion rate to the subsequent infusion rate after 2 hours based on patient tolerance. Total infusion time approximately 4-6 hours for day 1 and 6-8 hours for day 2. Subsequent infusion time is approximately 2 hours.

**RYBREVANT as a Single Agent**

- Administer RYBREVANT as a single agent infusion every 2 weeks intravenously according to the infusion rates in Table 8.
- Administer RYBREVANT via a peripheral line on Week 1 and Week 2, given the high incidence of infusion-related reactions during initial treatment (see Warnings and Precautions (5.1)).
- RYBREVANT may be administered via central line for subsequent weeks.
- For the initial infusion, prepare RYBREVANT as close to administration time as possible to allow for the possibility of extended infusion time in the event of an infusion related reaction.

**Table 8: Infusion Rates of RYBREVANT for Patients with Previously Treated NSCLC with Exon 20 Insertion Mutations (RYBREVANT as Single Agent)**

<table>
<thead>
<tr>
<th>Week</th>
<th>Dose (per 250 mL bag)</th>
<th>Initial Infusion Rate (mL/hr)</th>
<th>Subsequent Infusion Rate† (mL/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1 (split dose infusion)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 1 Day 1</td>
<td>350 mg</td>
<td>50</td>
<td>75</td>
</tr>
<tr>
<td>Week 1 Day 2</td>
<td>700 mg</td>
<td>50</td>
<td>75</td>
</tr>
<tr>
<td>Week 2</td>
<td>1050 mg</td>
<td></td>
<td>85</td>
</tr>
<tr>
<td>Week 3</td>
<td>1050 mg</td>
<td></td>
<td>125</td>
</tr>
<tr>
<td>Week 4</td>
<td>1050 mg</td>
<td></td>
<td>125</td>
</tr>
<tr>
<td>Week 5</td>
<td>1050 mg</td>
<td></td>
<td>125</td>
</tr>
<tr>
<td>Week 6</td>
<td>No dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 7 and every 2 weeks thereafter</td>
<td>1050 mg</td>
<td></td>
<td>125</td>
</tr>
</tbody>
</table>

1 In the absence of infusion-related reactions, increase the initial infusion rate to the subsequent infusion rate after 2 hours based on patient tolerance. Total infusion time approximately 4-6 hours for day 1 and 8-10 hours for day 2. Subsequent infusion time is approximately 2 hours.

3 DOSAGE FORMS AND STRENGTHS

Injection: 350 mg/7 mL (50 mg/mL) colorless to pale yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion-Related Reactions

RYBREVANT can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension and vomiting.

**RYBREVANT with Carboplatin and Pemetrexed**

RYBREVANT in combination with carboplatin and pemetrexed can cause infusion-related reactions. Based on the safety population (see Adverse Reactions (6.1)), infusion-related reactions occurred in 42% of patients treated with RYBREVANT in combination with carboplatin and pemetrexed, including Grade 3 (1.3%) adverse reactions. The incidence of infusion modifications due to IRR was 40%, and 0.7% of patients permanently discontinued RYBREVANT.

**RYBREVANT as a Single Agent**

Based on the safety population (see Adverse Reactions (6.1)), IRR occurred in 66% of patients treated with RYBREVANT as a single agent. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 34% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62%, and 1.3% of patients permanently discontinued RYBREVANT due to IRR.

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT as recommended (see Dosage and Administration (2.4)). Administer RYBREVANT via a peripheral line on Week 1 and Week 2 [see Dosage and Administration (2.7)].
Monitor patients for any signs and symptoms of infusion reactions during RYBREVANT infusion in a setting where cardiopulmonary resuscitation medication and equipment are available. Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVANT based on severity [see Dosage and Administration (2.5)].

5.2 Intestinal Lung Disease/Pneumonitis

RYBREVANT can cause intestinal lung disease (ILD)/pneumonitis.

• RYBREVANT with Carboplatin and Pemetrexed
Based on the safety population [see Adverse Reactions (6.1)], Grade 3 ILD/pneumonitis occurred in 2.6% of patients treated with RYBREVANT in combination with carboplatin and pemetrexed, all patients required inpatient hospitalization. RYBREVANT was permanently discontinued in 1% of patients. Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBREVANT in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed [see Dosage and Administration (2.5)].

5.3 Dermatologic Adverse Reactions

RYBREVANT can cause rash (including dermatitis acneeform), pruritus and dry skin.

• RYBREVANT with Carboplatin and Pemetrexed
RYBREVANT in combination with carboplatin and pemetrexed can cause dermatologic adverse reactions. Based on the safety population [see Adverse Reactions (6.1)], rash occurred in 74% of patients treated with RYBREVANT in combination with carboplatin and pemetrexed, including Grade 3 (19%) adverse reactions. Rash leading to dose reductions occurred in 19% of patients, and 2% permanently discontinued RYBREVANT. 1.3% discontinued pemetrexed.

• RYBREVANT as a Single Agent
Based on the safety population [see Adverse Reactions (6.1)], rash occurred in 74% of patients treated with RYBREVANT as a single agent, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 1 to 76 days). Rash leading to dose reduction occurred in 5% of patients, and RYBREVANT was permanently discontinued due to rash in 0.7% of patients [see Adverse Reactions (6.1)].

Toxic epidermal necrolysis (TEN) occurred in one patient (0.3%) treated with RYBREVANT as a single agent.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT. Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen. Alcohol-free emollient cream is recommended for dry skin. If skin reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity [see Dosage and Administration (2.6)].

5.4 Ocular Toxicity

RYBREVANT can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis.

• RYBREVANT with Carboplatin and Pemetrexed
RYBREVANT in combination with carboplatin and pemetrexed can cause ocular toxicity including blepharitis, dry eye, conjunctival redness, blurred vision, and eye pruritus. All events were Grade 1-2.

• RYBREVANT as a Single Agent
Based on the safety population [see Adverse Reactions (6.1)], keratitis occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBREVANT. All events were Grade 1-2. Promptly refer patients presenting with eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity [see Dosage and Administration (2.6)].

5.5 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal models, RYBREVANT can cause fetal harm when administered to a pregnant woman. Administration of other EGFR inhibitors molecules to pregnant animals has resulted in an increased incidence of implantation failures, embryonic-fetal development, embryo lethality, and abortion. Advise females of reproductive potential of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of RYBREVANT. [see Use in Specific Populations (8.1, 8.3)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

• Infusion-Related Reactions [see Warnings and Precautions (5.1)]
• Intestinal Lung Disease/Pneumonitis [see Warnings and Precautions (5.2)]
• Dermatologic Adverse Reactions [see Warnings and Precautions (5.3)]
• Ocular Toxicity [see Warnings and Precautions (5.4)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in the WARNINGS AND PRECAUTIONS reflect exposure to RYBREVANT in combination with carboplatin and pemetrexed in the PAPILLON study in 151 patients with locally advanced or metastatic NSCLC. Patients received RYBREVANT intravenously at 1400 mg (for patients <80 kg) or 1750 mg (for patients ≥80 kg) once weekly through 4 weeks, then every 3 weeks with a dose of 1750 mg (for patients <80 kg) or 2100 mg (for patients ≥80 kg) starting at Week 7 until disease progression or unacceptable toxicity, in combination with carboplatin at a dose under the curve AUC 5 once every 3 weeks, for up to 12 weeks, and pemetrexed at 500 mg/m2 once every 3 weeks until disease progression or unacceptable toxicity. Among 151 patients who received RYBREVANT in combination with carboplatin and pemetrexed, 76% were exposed for 6 months or longer and 38% were exposed for greater than one year. In the safety population, the most common (>20%) adverse reactions were rash, nail toxicity, stomatitis, infusion-related reaction, fatigue, constipation, and diarrhea. Among the most common laboratory abnormalities (>2%) were increased alanine aminotransferase decreased albumin, decreased potassium and decreased magnesium.

The data in the WARNINGS AND PRECAUTIONS also reflect exposure to RYBREVANT as a single agent in the CHRYSALIS study in 302 patients with locally advanced or metastatic NSCLC. Patients received RYBREVANT at 1050 mg (for patient baseline body weight <80 kg) or 1400 mg (for patient baseline body weight ≥80 kg) once weekly for 4 weeks, then every 2 weeks thereafter until disease progression or unacceptable toxicity. Among 302 patients who received RYBREVANT as a single agent, 36% were exposed for 6 months or longer and 12% were exposed for greater than one year. In the safety population, the most common (>20%) adverse reactions were rash, infusion-related reaction, paronychia, musculoskeletal pain, dyspnea, nausea, edema, cough, fatigue, stomatitis, constipation, vomiting and pruritus. The most common Grade 3 to 4 laboratory abnormalities (>2%) were increased gamma glutamyl transferase, decreased sodium, decreased potassium and increased alkaline phosphatase.

First-line Treatment of Non-Small Cell Lung Cancer (NSCLC) with Exon 20 Insertion Mutations

The data described below reflect exposure to RYBREVANT in combination with carboplatin and pemetrexed at the recommended dosage in the PAPILLON trial [see Clinical Studies (14.1)] in 151 patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations. Among patients who received RYBREVANT in combination with carboplatin and pemetrexed the median exposure was 9.7 months (range: 0.0 to 26.9 months). In patients that received carboplatin and pemetrexed alone, the median exposure was 6.7 months (range 0.0 to 25.3).

The median age was 61 years (range: 27 to 86 years); 56% were female; 64% were Asian, 32% were White, 1.3% were Black or African American, race was not reported in 1.3% of patients; 85% were not Hispanic or Latino; 86% had baseline body weight <80 kg. Serious adverse reactions occurred in 37% of patients who received RYBREVANT in combination with carboplatin and pemetrexed. Serious adverse reactions in ≥2% of patients included rash, pneumonia, interstitial lung disease (ILD), pulmonary embolism, vomiting and COVID-19. Fatal adverse reactions occurred in 7 patients (4.6%) due to pneumonia, cerebrovascular accident, cardio-respiratory arrest, COVID-19, sepsis and death not otherwise specified. Permanent discontinuation of RYBREVANT due to an adverse reaction occurred in 11% of patients. Adverse reactions resulting in permanent discontinuation of RYBREVANT in ≥1% of patients were rash and ILD.

Dose interruptions of RYBREVANT due to an adverse reaction occurred in 64% of patients. Infusion-related reactions (IRR) requiring infusion interruptions occurred in 38% of patients. Adverse reactions requiring dose interruption in ≥5% of patients included rash and nail toxicity.

Dose reductions of RYBREVANT due to an adverse reaction occurred in 36% of patients. Adverse reactions requiring dose reductions in ≥5% of patients included rash, and nail toxicity.

The most common adverse reactions (>20%) were rash, nail toxicity, stomatitis, infusion-related reaction, fatigue, edema, constipation, decreased appetite, nausea, COVID-19, diarrhea, and vomiting. The most common Grade 3 to 4 laboratory abnormalities (>2%) were decreased albumin, increased alanine aminotransferase, increased gamma-glutamyl transferase, decreased sodium, decreased potassium, decreased magnesium, and decreases in white blood cells, hemoglobin, neutrophils, platelets, and lymphocytes.
Table 9 summarizes the adverse reactions in PAPILLON. Adverse reactions were graded using CTCAE version 5.0. The denominator used to calculate the rate varied from 113 to 150 based on the number of patients with a baseline value and at least one post-treatment value. The denominator used to calculate the rate varied from 119 to 154 based on the number of patients with a baseline value and at least one post-treatment value.

Table 10: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients With Metastatic NSCLC with EGFR Exon 20 Insertion Mutations Who Received RYBREVANT in Combination with Carboplatin and Pemetrexed in PAPILLON.
Dose reductions of RYBREVANT due to an adverse reaction occurred in 15% of patients. Adverse reactions requiring dose reductions in ≥2% of patients included rash and paronychia.

The most common adverse reactions (≥20%) were rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting. The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased albumin, decreased phosphate, decreased potassium, increased glucose, increased alkaline phosphatase, increased gamma-glutamyl transferase, and decreased sodium.

Table 11 summarizes the adverse reactions in CHRYSALIS.

### Table 11: Adverse Reactions (≥10%) in Patients with NSCLC with Exon 20 Insertion Mutations Whose Disease Has Progressed on or after Platinum-based Chemotherapy and Received RYBREVANT in CHRYSALIS

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>RYBREVANT† (N=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>84</td>
</tr>
<tr>
<td>Pruritus</td>
<td>18</td>
</tr>
<tr>
<td>Dry skin</td>
<td>14</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>64</td>
</tr>
<tr>
<td>Fatigue*</td>
<td>33</td>
</tr>
<tr>
<td>Edema*</td>
<td>27</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>Paronychia</td>
<td>50</td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>10</td>
</tr>
<tr>
<td>Musculoskeletal pain and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>47</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Dyspnea*</td>
<td>37</td>
</tr>
<tr>
<td>Cough*</td>
<td>25</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>36</td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>26</td>
</tr>
<tr>
<td>Constipation</td>
<td>23</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
</tr>
<tr>
<td>Abdominal Pain*</td>
<td>11</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage*</td>
<td>19</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy*</td>
<td>13</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12</td>
</tr>
<tr>
<td>Headache*</td>
<td>10</td>
</tr>
</tbody>
</table>

*Adverse reactions were graded using CTCAE version 4.03

Clinically relevant adverse reactions in <10% of patients who received RYBREVANT included ocular toxicity, ILD/pneumonitis, and toxic epidermal necrolysis (TEN). Table 12 summarizes the laboratory abnormalities in CHRYSALIS.

### Table 12: Select Laboratory Abnormalities (≥20%) That Worsened from Baseline in Patients With Metastatic NSCLC with EGFR Exon 20 Insertion Mutations Whose Disease Has Progressed on or After Platinum-based Chemotherapy and Who Received RYBREVANT in CHRYSALIS

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>RYBREVANT* (N=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>79</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>56</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>53</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>46</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>38</td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>33</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>33</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>27</td>
</tr>
<tr>
<td>Increased gamma-glutamyl transferase</td>
<td>27</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>27</td>
</tr>
<tr>
<td>Decreased potassium</td>
<td>26</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>36</td>
</tr>
</tbody>
</table>

† The denominator used to calculate the rate was 126 based on the number of patients with a baseline value and at least one post-treatment value.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

**Risk Summary**

Based on the mechanism of action and findings in animal models, RYBREVANT can cause fetal harm when administered to a pregnant woman. There is no available data on the use of RYBREVANT in pregnant women or animal data to assess the risk of RYBREVANT in pregnancy. Disruption or depletion of EGFR in animal models resulted in impairment of embryo-fetal development including effects on placental, lung, cardiac, skin, and neural development. The absence of EGFR or MET signaling has resulted in embryolethality, malformations, and post-natal death in animals.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

**Data**

**Animal Data**

No animal studies have been conducted to evaluate the effects of amivantamab-vmjw on reproduction and fetal development; however, based on its mechanism of action, RYBREVANT can cause fetal harm or developmental anomalies. In mice, EGFR is critically important in reproductive and developmental processes including blastocyst implantation, placental development, and embryo-fetal/postnatal survival and development. Reduction or elimination of embryo-fetal or maternal EGFR signaling can prevent implantation, can cause embryo-fetal loss during various stages of gestation (through effects on placental development) and can cause developmental anomalies and early death in surviving fetuses. Adverse developmental outcomes were observed in multiple organs in embryos/neonates of mice with disrupted EGFR signaling. Similarly, knock out of MET or its ligand HGF was embryonic lethal due to severe defects in placental development, and fetuses displaying defects in muscle development in multiple organs. Human IgG1 is known to cross the placenta; therefore, amivantamab-vmjw has the potential to be transmitted from the mother to the developing fetus.

8.2 Lactation

**Risk Summary**

There are no data on the presence of amivantamab-vmjw in human milk, the effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions from RYBREVANT in breast-fed children, advise women not to breast-feed during treatment with RYBREVANT and for 3 months after the last dose.

8.3 Females and Males of Reproductive Potential

RYBREVANT can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

**Pregnancy Testing**

Verify pregnancy status of females of reproductive potential prior to initiating RYBREVANT.
RYBREVANT® (amivantamab-vmjw) injection

Contraception

Females
Adviser females of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of RYBREVANT.

8.4 Pediatric Use

The safety and efficacy of RYBREVANT have not been established in pediatric patients.

8.5 Geriatric Use

Of the 151 patients with locally advanced or metastatic NSCLC treated with RYBREVANT in combination with carboplatin and pemetrexed in the PAPILLON study, 37% were ≥65 years of age and 8% were ≥75 years of age.

Of the 302 patients with locally advanced or metastatic NSCLC treated with RYBREVANT as a single agent in the CHRYSALIS study, 39% were ≥65 years of age and 8% were ≥75 years of age.

No clinically important differences in safety or efficacy were observed between patients who were ≥65 years of age and younger patients.

11 DESCRIPTION

Amivantamab-vmjw is a low-fucose human immunoglobulin G1-based bispecific antibody directed against the EGFR and MET receptors, produced by mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology that has a molecular weight of approximately 148 kDa. RYBREVANT® (amivantamab-vmjw) injection for intravenous infusion is a sterile, preservative-free, colorless to pale yellow solution in single-dose vials. The pH is 5.7.

Each RYBREVANT vial contains 350 mg (50 mg/mL) amivantamab-vmjw, EDTA disodium salt dihydrate (0.14 mg), L-histidine (23.2 mg), L-histidine hydrochloride monohydrate (8.6 mg), L-methionine (7 mg), polyethylene glycol 80 (4.2 mg), sucrose (595 mg), and water for injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Amivantamab-vmjw is a bispecific antibody that binds to the extracellular domains of EGFR and MET.

In in vitro and in vivo studies amivantamab-vmjw was able to disrupt EGFR and MET signaling functions through blocking ligand binding and, in exon 20 insertion mutation models, degradation of EGFR and MET. The presence of EGFR and MET on the surface of tumor cells also allows for targeting of these cells for destruction by immune effector cells, such as natural killer cells and macrophages, through antibody-dependent cellular cytotoxicity (ADCC) and tregocytosis mechanisms, respectively.

12.2 Pharmacodynamics

The exposure-response relationship and time-course of pharmacodynamic response of amivantamab-vmjw have not been fully characterized in patients with NSCLC with EGFR exon 20 insertion mutations.

12.3 Pharmacokinetics

Based on RYBREVANT single agent data, amivantamab-vmjw exposures increased proportionally over a dosage range from 350 to 1750 mg. Based on the population pharmacokinetics of RYBREVANT, steady-state concentrations of RYBREVANT were reached by week 13 for both the 3-week and 2-week dosing regimen and the systemic accumulation was 1.9-fold.

Distribution

The amivantamab-vmjw mean (± SD) volume of distribution is 5.34 (± 1.81) L.

Elimination

The geometric mean (% CV) linear clearance (CL) and terminal half-life is 0.266 L/day (30.4%) and 13.7 days (31.9%), respectively.

Specific Populations

No clinically meaningful differences in the pharmacokinetics of amivantamab-vmjw were observed based on age (range: 27-87 years), sex, race, creatinine clearance (CLcr 29 to 101 mL/min), or mild hepatic impairment ([total bilirubin ≤ ULN and AST > ULN] or [ULN < total bilirubin ≤ 1.5 times ULN]). The pharmacokinetics of amivantamab-vmjw have not been studied in patients with severe renal impairment (CLcr 15 to 29 mL/min) or patients with moderate (total bilirubin 1.5 to 3 times ULN) to severe (total bilirubin > 3 times ULN) hepatic impairment.

Body Weight

Increases in body weight increased the volume of distribution and clearance of amivantamab-vmjw. Amivantamab-vmjw exposures are 30-40% lower in patients who weighed ≥ 80 kg compared to patients with body weight < 80 kg at the same dose. Exposures of amivantamab-vmjw were comparable between patients who weighed < 80 kg and received 1050 mg dose and patients who weighed ≥ 80 kg and received 1400 mg dose.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies (ADA) in the studies described below with the incidence of anti-drug antibodies in other studies, including those of amivantamab-vmjw or amivantamab products.

In patients with NSCLC who received RYBREVANT as a single agent or as part of a combination therapy, 3 of the 663 (0.5%) patients who were treated with RYBREVANT and evaluable for the presence of anti-drug antibodies (ADA) tested positive for treatment-emergent anti-amivantamab-vmjw antibodies. Given the low incidence of detectable antibody-drug antibodies, the effect of ADA on the efficacy of RYBREVANT remains unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to assess the potential of amivantamab-vmjw for carcinogenicity or genotoxicity. Fertility studies have not been performed to evaluate the potential effects of amivantamab-vmjw. In 6-week and 3-month repeat-dose toxicity studies in monkeys, there were no notable effects in the male and female reproductive organs.

14 CLINICAL STUDIES

14.1 First Line Treatment of NSCLC with Exon 20 Insertion Mutations-PAPILLON

The efficacy of RYBREVANT was evaluated in PAPILLON (NCT04538664), in a randomized, open-label, multicenter study. Eligible patients were required to have previously untreated locally advanced or metastatic NSCLC with EGFR Exon 20 insertion mutations measurable disease per RECIST v1.1, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1, and adequate organ and bone marrow function. Patients with brain metastases at screening were eligible for participation once they were definitively treated, clinically stable, asymptomatic, and off corticosteroid treatment for at least 2 weeks prior to randomization. Patients with a medical history of interstitial lung disease or active ILD were excluded from the clinical study.

A total of 308 patients were randomized 1:1 to receive RYBREVANT in combination with carboplatin and pemetrexed (n=153) or carboplatin and pemetrexed (n=155). Patients received RYBREVANT intravenously at 1400 mg (for patients < 80 kg) or 1750 mg (for patients ≥ 80 kg) once weekly through 4 weeks, then every 3 weeks with a dose of 1750 mg (for patients < 80 kg) or 2100 mg (for patients ≥ 80 kg) starting at Week 7 until disease progression or unacceptable toxicity. Carboplatin was administered intravenously at area under the concentration-time curve 5 mg/mL per minute (AUC 5) once every 3 weeks, for up to 12 weeks. Pemetrexed was administered intravenously at 500 mg/m² on once every 3 weeks until disease progression or unacceptable toxicity. Patients were stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1) and prior brain metastases (yes or no).

The primary efficacy outcome measure was progression-free survival (PFS) as assessed by blinded independent central review (BICR). Additional efficacy outcome measures included overall response rate (ORR), duration of response (DOR) and overall survival (OS). Cross-over to single agent RYBREVANT was permitted for patients who had confirmed disease progression on carboplatin and pemetrexed.

The median age was 62 (range: 27 to 92) years, with 40% of the patients ≥ 65 years of age; 58% were female; 61% were Asian and 36% were White, 0.7% were Black or African American and race was not reported in 2.3% of patients; 93% were not Hispanic or Latino. Baseline ECOG performance status was 0 (35%) or 1 (65%); 58% were never smokers; 23% had history of brain metastasis and 84% had Stage IV cancer at initial diagnosis.

PAPILLON demonstrated a statistically significant improvement in progression free survival for patients randomized to RYBREVANT in combination with carboplatin and pemetrexed compared with carboplatin and pemetrexed. Efficacy results are summarized in Table 13 and Figure 1.

Table 13: Efficacy Results in PAPILLON

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RYBREVANT+ carboplatin+ pemetrexed (N=153)</th>
<th>carboplatin+ pemetrexed (N=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events (%)</td>
<td>84 (55)</td>
<td>132 (85)</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>11.4 (9.8, 13.7)</td>
<td>6.7 (5.6, 7.3)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.40 (0.30, 0.53)</td>
<td>p-value 0.0001</td>
</tr>
</tbody>
</table>
| Overall Response Rate (ORR)
| ORR, (95% CI) | 67 (59, 75) | 36 (29, 44) |
| Complete response, % | 4 | 1 |
| Partial response, % | 63 | 36 |
| Duration of response (DOR)
| Median (95% CI), months | 10.1 (6.5, 13.9) | 5.6 (4.4, 6.9) |

CI = confidence interval
¹ Confirmed responses.
² In confirmed responders.
Table 14: Efficacy Results for CHRYSALIS

<table>
<thead>
<tr>
<th>Prior Platinum-based Chemotherapy Treated (N=81)</th>
<th>Overall Response Rate (95% CI)</th>
<th>40% (29%, 51%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete response (CR)</td>
<td>3.7%</td>
</tr>
<tr>
<td></td>
<td>Partial response (PR)</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td>Duration of Response (DOR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median, months (95% CI), months</td>
<td>11.1 (6.9, NE)</td>
</tr>
<tr>
<td></td>
<td>Patients with DOR ≥6 months</td>
<td>63%</td>
</tr>
</tbody>
</table>

Based on Kaplan-Meier estimates. NE=Not Estimable, CI=confidence interval.

While OS results were immature at the current analysis, with 44% of pre-specified deaths for the final analysis reported, no trend towards a detriment was observed. Seventy-five (46%) of the treated patients crossed over from the carboplatin and pemetrexed arm after confirmation of disease progression to receive RYBREVANT as a single agent.

14.2 Previously Treated NSCLC with Exon 20 Insertion Mutations-CHRYSALIS

The efficacy of RYBREVANT was evaluated in patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations in a multicenter, open-label, multi-cohort clinical trial (CHRYSALIS, NCT02609776). The study included patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations whose disease had progressed on or after platinum-based chemotherapy. Patients with untreated brain metastases and patients with a history of ILD requiring treatment with prolonged steroids or other immunosuppressive agents within the last 2 years were not eligible for the study.

In the efficacy population, EGFR exon 20 insertion mutation status was determined by prospective local testing using tissue (94%) and/or plasma (6%) samples. Of the 81 patients with EGFR exon 20 insertion mutations identified by local testing, plasma samples from 78/81 (96%) patients were tested retrospectively using Guardant360® CDx, identifying 62/78 (79%) samples with an EGFR exon 20 insertion mutation; 16/78 (21%) samples did not have an EGFR exon 20 insertion mutation identified.

Patients received RYBREVANT at 1050 mg (for patient baseline body weight < 80 kg) or 1400 mg (for patient baseline body weight ≥ 80 kg) once weekly for 4 weeks, then every 2 weeks thereafter until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by Blinded Independent Central Review (BICR). An additional efficacy outcome measure was duration of response (DOR) by BICR.

The efficacy population included 81 patients with NSCLC with EGFR exon 20 insertion mutation with measurable disease who were previously treated with platinum-based chemotherapy. The median age was 62 (range: 42 to 84) years, 59% were female; 49% were Asian, 37% were White, 2.5% were Black; 74% had baseline body weight < 80 kg; 95% had adenocarcinoma; and 46% had received platinum-based chemotherapy. The median number of prior therapies was 2 (range: 1 to 7). At baseline, 67% had Eastern Cooperative Oncology Group (ECOG) performance status of 1; 53% never smoked; all patients had metastatic disease; and 22% had previously treated brain metastases.

Efficacy results are summarized in Table 14.
What is RYBREVANT?
RYBREVANT is a prescription medicine used to treat adults:

- in combination with carboplatin and pemetrexed as a first-line treatment for non-small cell lung cancer (NSCLC) that:
  - has spread to other parts of the body (metastatic) or cannot be removed by surgery, and
  - has a certain abnormal epidermal growth factor receptor “EGFR” gene(s)
- alone for the treatment of non-small cell lung cancer (NSCLC) that:
  - has spread to other parts of the body (metastatic) or cannot be removed by surgery, and
  - has a certain abnormal EGFR gene(s), whose disease has worsened on or after platinum-based chemotherapy.

Your healthcare provider will perform a test to make sure that RYBREVANT is right for you.

It is not known if RYBREVANT is safe and effective in children.

Before you receive RYBREVANT, tell your healthcare provider about all of your medical conditions, including if you:

- have a history of lung or breathing problems
- are pregnant or plan to become pregnant. RYBREVANT can harm your unborn baby.

**Females who are able to become pregnant:**
- Your healthcare provider should do a pregnancy test before you start treatment with RYBREVANT.
- You should use effective birth control (contraception) during treatment and for 3 months after your last dose of RYBREVANT.
- Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with RYBREVANT.

- are breastfeeding or plan to breastfeed. It is not known if RYBREVANT passes into your breast milk. Do not breastfeed during treatment and for 3 months after your last dose of RYBREVANT.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive RYBREVANT?

- RYBREVANT will be given to you by your healthcare provider by intravenous infusion into your vein.
- Your healthcare provider will decide the time between doses as well as how many treatments you will receive.
- Your healthcare provider will give you medicines before each dose of RYBREVANT to help reduce the risk of infusion-related reactions.
- RYBREVANT may be given in combination with the medicines carboplatin and pemetrexed. If you have any questions about these medicines, ask your healthcare provider.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What should I avoid while receiving RYBREVANT?
RYBREVANT can cause skin reactions. You should limit your time in the sun during and for 2 months after your treatment with RYBREVANT. Wear protective clothing and use sunscreen during treatment with RYBREVANT.
What are the possible side effects of RYBREVANT?
RYBREVANT may cause serious side effects, including:

- **infusion-related reactions.** Infusion-related reactions are common with RYBREVANT and can be severe or serious. Tell your healthcare provider right away if you get any of the following symptoms during your infusion of RYBREVANT:
  - shortness of breath
  - fever
  - chills
  - nausea
  - flushing
  - chest discomfort
  - lightheadedness
  - vomiting

- **lung problems.** RYBREVANT may cause lung problems that may lead to death. Symptoms may be similar to those symptoms from lung cancer. Tell your healthcare provider right away if you get any new or worsening lung symptoms, including shortness of breath, cough, or fever.

- **skin problems.** RYBREVANT may cause rash, itching, and dry skin. You may use alcohol-free moisturizing cream for dry skin. Tell your healthcare provider right away if you get any skin reactions. Your healthcare provider may treat you with a medicine(s) or send you to see a skin specialist (dermatologist) if you get skin reactions during treatment with RYBREVANT. See “What should I avoid while receiving RYBREVANT?”

- **eye problems.** RYBREVANT may cause eye problems. Tell your healthcare provider right away if you get symptoms of eye problems which may include:
  - eye pain
  - dry eyes
  - eye redness
  - blurred vision
  - changes in vision
  - itchy eyes
  - excessive tearing
  - sensitivity to light

Your healthcare provider may send you to see an eye specialist (ophthalmologist) if you get eye problems during treatment with RYBREVANT. You should not use contact lenses until your eye symptoms are checked by a healthcare provider.

The most common side effects of RYBREVANT in combination with carboplatin and pemetrexed include:

- rash
- infected skin around the nail
- sores in the mouth
- infusion-related reactions
- feeling very tired
- swelling of hands, ankles, feet, face, or all of your body
- constipation
- decreased appetite
- nausea
- COVID-19
- diarrhea
- vomiting
- changes in certain blood tests

The most common side effects of RYBREVANT when given alone:

- rash
- infusion-related reactions
- infected skin around the nail
- muscle and joint pain
- shortness of breath
- nausea
- feeling very tired
- swelling of hands, ankles, feet, face, or all of your body
- sores in the mouth
- cough
- constipation
- vomiting
- changes in certain blood tests

Your healthcare provider may temporarily stop, decrease your dose or completely stop your treatment with RYBREVANT if you have serious side effects.

These are not all of the possible side effects of RYBREVANT.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
**General information about safe and effective use of RYBREVANT**
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your healthcare provider or pharmacist for information about RYBREVANT that is written for health professionals.

**What are the ingredients of RYBREVANT?**
**Active ingredient:** amivantamab-vmjw  
**Inactive ingredients:** EDTA disodium salt dihydrate, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 80, sucrose, and water for injection.

Product of Ireland  
Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, USA. U.S. License Number 1864  
For patent information: www.janssenpatents.com  
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For more information, call 1-800-526-7736 (1-800-JANSSEN) or go to www.RYBREVANT.com.

This Patient Information has been approved by the U.S. Food and Drug Administration.  
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