# RYBREVANT®
## (amivantamab-vmjw)

Injection for IV Use | 350 mg/7 mL (50 mg/mL)

# Dosing and Administration Guide

INDICATION

RYBREVANT® is a bispecific EGF receptor-directed and MET receptor-directed antibody indicated 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 mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

**Please see full Important Safety Information on pages 18-19 and please click here to read full RYBREVANT® Prescribing Information.**

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## What is RYBREVANT®?

RYBREVANT® is a bispecific EGF receptor-directed and MET receptor-directed antibody indicated 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 mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

## How RYBREVANT® Works

RYBREVANT® is a bispecific antibody that binds to the extracellular domains of EGFR and MET.

In *in vitro* and *in vivo* studies RYBREVANT® 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 trogocytosis mechanisms, respectively.

EGFR, epidermal growth factor receptor; MET, Mesenchymal-Epithelial Transition.

## IMPORTANT SAFETY INFORMATION

### WARNINGS AND PRECAUTIONS

**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.

Based on the safety population, IRR occurred in 66% of patients treated with RYBREVANT®. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% 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.

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## RYBREVANT® Was Studied in the CHRYSALIS Trial

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, plasma samples from 96% of patients were tested retrospectively using Guardant360® CDx. While 76% of patients had an EGFR exon 20 insertion mutation identified in plasma specimen, 20% did not have an EGFR exon 20 insertion mutation identified in plasma specimen, and 3.7% did not have plasma samples for testing.

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 prior immunotherapy. 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.

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## RYBREVANT® Efficacy

Table 9: Efficacy Results for CHRYSALIS

| | Prior Platinum-based Chemotherapy Treated (N=81) |
|---|---|
| **Overall response rate** (95% CI) | 40% (29%, 51%) |
| Complete response (CR) | 3.7% |
| Partial response (PR) | 36% |
| **Duration of response (DOR)** | |
| Median, months (95% CI), months | 11.1 (6.9, NE) |
| Patients with DOR ≥6 months | 63% |

Based on Kaplan-Meier estimates.
CI=confidence interval, NE=not estimable.

### IMPORTANT SAFETY INFORMATION

**Infusion-Related Reactions (cont'd)**

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT® as recommended. Administer RYBREVANT® via a peripheral line on Week 1 and Week 2. 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.

**Interstitial Lung Disease/Pneumonitis**

RYBREVANT® can cause interstitial lung disease (ILD)/pneumonitis. Based on the safety population, ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT®, with 0.7% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBREVANT® due to ILD/pneumonitis.

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.

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## RYBREVANT® Recommended Dosage

The recommended doses of RYBREVANT®, based on baseline body weight, are provided in Table 1, and the dosing schedule is provided in Table 2. Administer premedications before each RYBREVANT® infusion as recommended. Administer diluted RYBREVANT® intravenously according to the infusion rates in Table 6, with the initial dose as a split infusion on Week 1 on Day 1 and Day 2. Administer RYBREVANT® until disease progression or unacceptable toxicity.

Table 1: Recommended Dose of RYBREVANT® Based on Baseline Body Weight

| Body Weight at Baseline* | Recommended Dose | Number of 350 mg/7 mL RYBREVANT® Vials |
|---|---|---|
| **Less than 80 kg** | 1050 mg | 3 |
| **Greater than or equal to 80 kg** | 1400 mg | 4 |

*Dosage adjustments not required for subsequent body weight changes.

***Select patients for treatment with RYBREVANT® based on the presence of EGFR exon 20 insertion mutations.***

Information on FDA-approved companion diagnostic tests is available at http://www.fda.gov/CcompanionDiagnostics.

Table 2: Dosing Schedule for RYBREVANT®

| Weeks | Schedule |
|---|---|
| **Week 1 to 4** | Weekly (total of 4 doses) |
| | Week 1 - split infusion on Day 1 and Day 2 |
| | Weeks 2 to 4 - Infusion on Day 1 |
| **Week 5 onwards** | Every 2 weeks starting at Week 5 |

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## Serious and Most Common Adverse Reactions

Serious adverse reactions occurred in 30% of patients who received RYBREVANT®. Serious adverse reactions in ≥2% of patients included pulmonary embolism, pneumonitis/ILD, dyspnea, musculoskeletal pain, pneumonia, and muscular weakness. Fatal adverse reactions occurred in 2 patients (1.5%) due to pneumonia and 1 patient (0.8%) due to sudden death.

The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%). The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphate (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and decreased sodium (4%).

## IMPORTANT SAFETY INFORMATION

**Dermatologic Adverse Reactions**

RYBREVANT® can cause rash (including dermatitis acneiform), pruritus and dry skin. Based on the safety population, rash occurred in 74% of patients treated with RYBREVANT®, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYBREVANT® was permanently discontinued due to rash in 0.7% of patients.

Toxic epidermal necrolysis occurred in one patient (0.3%) treated with RYBREVANT®.

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. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce or permanently discontinue RYBREVANT® based on severity.

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## RYBREVANT® Administration

Administer the diluted solution 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) primed with diluent only. Administration sets must be made of either polyurethane (PU), polybutadiene (PBD), PVC, PP, or PE.

Do not infuse RYBREVANT® concomitantly in the same intravenous line with other agents.

Administer RYBREVANT® via a peripheral line on Week 1 and Week 2 given the high incidence of infusion-related reactions during initial treatment. 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.

PE, polyethylene; PP, polypropylene; PVC, polyvinylchloride.

## IMPORTANT SAFETY INFORMATION

**Ocular Toxicity**
RYBREVANT® can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis. Based on the safety population, 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.

**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. 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 final dose of RYBREVANT®.

Table 6: Infusion Rates for RYBREVANT® Administration

| 1050 mg Dose (<80 kg) | | | |
|---|---|---|---|
| **Week** | **Dose (per 250 mL bag)** | **Initial infusion rate** | **Subsequent infusion rate†** |
| **Week 1 (split dose infusion)** | | | |
| Week 1 *Day 1* | 350 mg | 50 mL/hr | 75 mL/hr |
| Week 1 *Day 2* | 700 mg | 50 mL/hr | 75 mL/hr |
| **Week 2** | 1050 mg | 85 mL/hr | |
| **Week 3** | 1050 mg | 125 mL/hr | |
| **Week 4** | 1050 mg | 125 mL/hr | |
| **Subsequent weeks*** | 1050 mg | 125 mL/hr | |

| 1400 mg Dose (≥80 kg) | | | |
|---|---|---|---|
| **Week** | **Dose (per 250 mL bag)** | **Initial infusion rate** | **Subsequent infusion rate†** |
| **Week 1 (split dose infusion)** | | | |
| Week 1 *Day 1* | 350 mg | 50 mL/hr | 75 mL/hr |
| Week 1 *Day 2* | 1050 mg | 35 mL/hr | 50 mL/hr |
| **Week 2** | 1400 mg | 65 mL/hr | |
| **Week 3** | 1400 mg | 85 mL/hr | |
| **Week 4** | 1400 mg | 125 mL/hr | |
| **Subsequent weeks*** | 1400 mg | 125 mL/hr | |

*Starting at Week 5, patients are dosed every 2 weeks.

†Increase the initial infusion rate to the subsequent infusion rate after 2 hours in the absence of infusion-related reactions.

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## Recommended Premedications

- Prior to initial infusion of RYBREVANT® (Week 1, Days 1 and 2), administer premedication as described in Table 3 to reduce the risk of infusion-related reactions
- Administer both antihistamine and antipyretic prior to all infusions
- Glucocorticoid administration required for Week 1, Days 1 and 2 doses only and as necessary for subsequent infusions

Table 3: Premedications

| Medication | Dose | Route of Administration | Dosing Window Prior to RYBREVANT® Administration |
|---|---|---|---|
| Antihistamine* | Diphenhydramine (25 to 50 mg) or equivalent | Intravenous | 15 to 30 minutes |
| | | Oral | 30 to 60 minutes |
| Antipyretic* | Acetaminophen (650 to 1000 mg) | Intravenous | 15 to 30 minutes |
| | | Oral | 30 to 60 minutes |
| Glucocorticoid‡ | Dexamethasone (10 mg) or Methylprednisolone (40 mg) or equivalent | Intravenous | 45 to 60 minutes |

*Required at all doses.
‡Required at initial dose (Week 1, Days 1 and 2); optional for subsequent doses.

**IMPORTANT SAFETY INFORMATION**

**Adverse Reactions**
The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%). The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphate (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and decreased sodium (4%).

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## RYBREVANT® Preparation

Dilute and prepare RYBREVANT® for intravenous infusion before administration.

- Check that the RYBREVANT® 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 discoloration or visible particles are present.
- Determine the dose required (either 1050 mg or 1400 mg) and number of RYBREVANT® vials needed based on patient's baseline weight. Each vial of RYBREVANT® 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 RYBREVANT® to be added (i.e., discard 7 mL diluent from the infusion bag for each RYBREVANT® vial). Only use infusion bags made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE), or polyolefin blend (PP+PE).
- Withdraw 7 mL of RYBREVANT® 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).

## Recommended RYBREVANT® Dosage Modifications for Infusion-Related Reactions (IRRs)

### Grade 1-2

- Interrupt RYBREVANT® 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 Table 6)
- Include corticosteroid with premedications for subsequent dose

### Grade 3

- Interrupt RYBREVANT® infusion and administer supportive care medications. 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 Table 6)
- Include corticosteroid with premedications for subsequent dose (see Table 3). For recurrent Grade 3, permanently discontinue RYBREVANT®

### Grade 4

- Permanently discontinue RYBREVANT®

## 97% of IRRs Were Grade 1-2

- IRRs occurred in 66% of patients treated with RYBREVANT®
- Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions
- The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion
- Signs and symptoms include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting
- 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

## IMPORTANT SAFETY INFORMATION

**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.

Based on the safety population, IRR occurred in 66% of patients treated with RYBREVANT®. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% 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.

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## RYBREVANT® Dosage Modifications for Adverse Reactions

The recommended RYBREVANT® dose reductions for adverse reactions (see Table 5) are listed in Table 4.

### Table 4: RYBREVANT® Dose Reductions for Adverse Reactions

| Body Weight at Baseline | Initial Dose | 1st Dose Reduction | 2nd Dose Reduction | 3rd Dose Reduction |
|---|---|---|---|---|
| **Less than 80 kg** | 1050 mg | 700 mg | 350 mg | Discontinue RYBREVANT® |
| **Greater than or equal to 80 kg** | 1400 mg | 1050 mg | 700 mg | |

## IMPORTANT SAFETY INFORMATION

**Infusion-Related Reactions (cont'd)**

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT® as recommended. Administer RYBREVANT® via a peripheral line on Week 1 and Week 2. 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.

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The recommended RYBREVANT® dosage modifications for adverse reactions are provided in Table 5.

### Table 5: Recommended RYBREVANT® Dosage Modifications for Adverse Reactions

| Adverse Reaction | Severity | Dosage Modifications |
|---|---|---|
| **Infusion-related reactions (IRR)** | Grade 1 to 2 | • Interrupt RYBREVANT® infusion if IRR is suspected and monitor patient until reaction symptoms resolve<br>• Resume the infusion at 50% of the infusion rate at which the reaction occurred<br>• If there are no additional symptoms after 30 minutes, the infusion rate may be escalated (see Table 6)<br>• Include corticosteroid with premedications for subsequent dose (see Table 3) |
| | Grade 3 | • Interrupt RYBREVANT® infusion and administer supportive care medications. Monitor patient until reaction symptoms resolve<br>• Resume the infusion at 50% of the infusion rate at which the reaction occurred<br>• If there are no additional symptoms after 30 minutes, the infusion rate may be escalated (see Table 6)<br>• Include corticosteroid with premedications for subsequent dose (see Table 3). For recurrent Grade 3, permanently discontinue RYBREVANT® |
| | Grade 4 | • Permanently discontinue RYBREVANT® |
| **Interstitial Lung Disease (ILD)/ pneumonitis** | Any Grade | • Withhold RYBREVANT® if ILD/pneumonitis is suspected<br>• Permanently discontinue RYBREVANT® if ILD/ pneumonitis is confirmed |
| **Dermatologic Adverse Reactions (including dermatitis acneiform, pruritus, dry skin)** | Grade 2 | • Initiate supportive care management<br>• Reassess after 2 weeks; if rash does not improve, consider dose reduction |
| | Grade 3 | • Withhold RYBREVANT® and initiate supportive care management<br>• Upon recovery to ≤ Grade 2, resume RYBREVANT® at reduced dose<br>• If no improvement within 2 weeks, permanently discontinue treatment |
| | Grade 4 | • Permanently discontinue RYBREVANT® |
| | Severe bullous, blistering or exfoliating skin conditions [including toxic epidermal necrolysis (TEN)] | • Permanently discontinue RYBREVANT® |
| **Other Adverse Reactions** | Grade 3 | • Withhold RYBREVANT® until recovery to ≤Grade 1 or baseline<br>• Resume at the same dose if recovery occurs within 1 week<br>• Resume at reduced dose if recovery occurs after 1 week but within 4 weeks<br>• Permanently discontinue if recovery does not occur within 4 weeks |
| | Grade 4 | • Withhold RYBREVANT® until recovery to ≤Grade 1 or baseline<br>• Resume at reduced dose if recovery occurs within 4 weeks<br>• Permanently discontinue if recovery does not occur within 4 weeks<br>• Permanently discontinue for recurrent Grade 4 reactions |

## How RYBREVANT® Is Supplied


- RYBREVANT® (amivantamab-vmjw) injection is a sterile, preservative-free, colorless to pale yellow solution for intravenous infusion. Each single-dose vial contains 350 mg/7 mL (50 mg/mL) RYBREVANT®. Each vial is individually packed in a single carton. (NDC 57894-501-01)
- Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in original carton to protect from light
- Do not freeze RYBREVANT®

## IMPORTANT SAFETY INFORMATION

**Adverse Reactions**

The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%). The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphate (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and decreased sodium (4%).

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## Patient Counseling Information

Advise the patient to read the FDA-approved patient labeling (Patient Information), as applicable.

| | |
|---|---|
| **Infusion-Related Reactions** | Advise patients that RYBREVANT® can cause infusion-related reactions, the majority of which may occur with the first infusion. Advise patients to alert their healthcare provider immediately for any signs or symptoms of infusion-related reactions. |
| **Interstitial Lung Disease/ Pneumonitis** | Advise patients of the risks of interstitial lung disease (ILD)/pneumonitis. Advise patients to immediately contact their healthcare provider for new or worsening respiratory symptoms. |
| **Dermatologic Adverse Reactions** | Advise patients of the risk of dermatologic adverse reactions. Advise patients to limit direct sun exposure, to use broad spectrum UVA/UVB sunscreen, and to wear protective clothing during treatment with RYBREVANT®. Advise patients to apply alcohol free emollient cream to dry skin. |
| **Ocular Toxicity** | Advise patients of the risk of ocular toxicity. Advise patients to contact their ophthalmologist if they develop eye symptoms and advise discontinuation of contact lenses until symptoms are evaluated. |
| **Paronychia** | Advise patients of the risk of paronychia. Advise patients to contact their healthcare provider for signs and symptoms of paronychia. |
| **Embryo-Fetal Toxicity** | Advise females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment with RYBREVANT® and for 3 months after the final dose, and to inform their healthcare provider of a known or suspected pregnancy. |
| **Lactation** | Advise women not to breastfeed during treatment with RYBREVANT® and for 3 months after the final dose. |

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## Indication and Important Safety Information

### INDICATION

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This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

### IMPORTANT SAFETY INFORMATION

### WARNINGS AND PRECAUTIONS

**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.

Based on the safety population, IRR occurred in 66% of patients treated with RYBREVANT®. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% 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. Administer RYBREVANT® via a peripheral line on Week 1 and Week 2. 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.

**Interstitial Lung Disease/Pneumonitis**
RYBREVANT® can cause interstitial lung disease (ILD)/pneumonitis. Based on the safety population, ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT®, with 0.7% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBREVANT® due to ILD/pneumonitis.

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.

**Dermatologic Adverse Reactions**
RYBREVANT® can cause rash (including dermatitis acneiform), pruritus and dry skin. Based on the safety population, rash occurred in 74% of patients treated with RYBREVANT®, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYBREVANT® was permanently discontinued due to rash in 0.7% of patients.

Toxic epidermal necrolysis occurred in one patient (0.3%) treated with RYBREVANT®.

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. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce or permanently discontinue RYBREVANT® based on severity.

**Ocular Toxicity**
RYBREVANT® can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis. Based on the safety population, 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.

**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. 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 final dose of RYBREVANT®.

**Adverse Reactions**
The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%). The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphate (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and decreased sodium (4%).

**Please read full Prescribing Information for RYBREVANT®.**

cp-213274v2

## Infusion Checklist

### Pre-infusion

- Prior to initial infusion of RYBREVANT® (Week 1, Days 1 and 2), administer premedication as described in Table 3 to reduce the risk of infusion-related reactions
- Administer both antihistamine and antipyretic prior to all infusions
- Glucocorticoid administration required for Week 1, Days 1 and 2 doses only and as necessary for subsequent infusions
- Do not infuse RYBREVANT® concomitantly in the same intravenous line with other agents
- Administer RYBREVANT® via a peripheral line on Week 1 and Week 2 given the high incidence of infusion-related reactions during initial treatment. RYBREVANT® may be administered via central line for subsequent weeks

### During the Infusion

√ 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

√ Administer RYBREVANT® infusion intravenously according to the infusion rates on page 9

Based on the safety population, IRR occurred in 66% of patients treated with RYBREVANT®. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions

**Please see full Important Safety Information on pages 18-19 and click here to read full RYBREVANT® Prescribing Information**



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