

## PRODUCT NAME

RYBREVANT<sup>®</sup> (amivantamab) concentrate for solution for infusion

## DOSAGE FORMS AND STRENGTHS

Amivantamab is a fully-human immunoglobulin G1(IgG1)-based bispecific antibody directed against the epidermal growth factor (EGF) and mesenchymal-epidermal transition (MET) receptors, produced by a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology (see *Pharmacodynamic Properties - Mechanism of action*).

RYBREVANT<sup>®</sup> is available as a colorless to pale yellow preservative-free liquid concentrate for intravenous infusion after dilution.

Each single-use vial contains 350 mg of amivantamab per 7 mL vial (or 50 mg of amivantamab per mL).

For excipients, see *List of Excipients*.

## CLINICAL INFORMATION

### Indications

RYBREVANT<sup>®</sup> is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal-growth factor receptor (EGFR) Exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy.

### Dosage and Administration

RYBREVANT<sup>®</sup> should be administered by a healthcare professional with appropriate medical support to manage infusion-related reactions (IRRs) if they occur (see *Warnings and Precautions*).

Administer pre-infusion medications (see *Dosage and Administration – Pre-infusion medications*).

When considering the use of RYBREVANT<sup>®</sup>, EGFR Exon 20 insertion mutation presence should be established using a validated test (see *Pharmacodynamic Effects - Clinical studies*).

### Dosage – adults (≥18 years)

The recommended dose of RYBREVANT<sup>®</sup> is provided in Table 1, and the dosing schedule is provided in Table 2 (see *Infusion Rates – Table 4*).

**Table 1: Recommended Dose of RYBREVANT<sup>®</sup>**

Body Weight of Patient (at Baseline*)	Recommended Dose	Number of 350 mg/7 mL RYBREVANT <sup>®</sup> Vials
Less than 80 kg	1050 mg	3
Greater than or equal to 80 kg	1400 mg	4

\* Dose adjustments not required for subsequent body weight changes.

**Table 2: Dosing Schedule for RYBREVANT®**

Weeks	Schedule
Weeks 1 to 4	Weekly (total of 4 doses)
Week 5 onwards	Every 2 weeks starting at Week 5

It is recommended that patients are treated with RYBREVANT® until unacceptable toxicity or disease progression.

### ***Pre-infusion medications***

Prior to initial infusion of RYBREVANT® (Week 1, Days 1 and 2), administer antihistamines, antipyretics, and glucocorticoids to reduce the risk of IRRs. For subsequent doses, administer antihistamines and antipyretics. Administer antiemetics as needed.

**Table 3: Pre-Medications**

Medication	Dose	Route of Administration	Dosing Window Prior to RYBREVANT® Administration
Antihistamine*	Diphenhydramine (25 to 50 mg) or equivalent	IV	15 to 30 minutes
		Oral	30 to 60 minutes
Antipyretic*	Paracetamol/Acetaminophen (650 to 1,000 mg) or equivalent	IV	15 to 30 minutes
		Oral	30 to 60 minutes
Glucocorticoid‡	Dexamethasone (10 mg) or Methylprednisolone (40 mg) or equivalent	IV	45 to 60 minutes

\* Required at all doses.

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

### ***Infusion Rates***

Administer RYBREVANT® infusion intravenously according to the infusion rates in Table 4. Due to the frequency of IRRs at the first dose, infusion via a peripheral vein at Week 1 and Week 2 should be considered to minimize drug exposure in the event of an IRR; infusion via central line may be administered for subsequent weeks. It is recommended for the first dose to be diluted as close to administration as possible to allow for maximal flexibility in IRR management.

**Table 4: Infusion Rates for RYBREVANT® Administration**

1050 mg Dose			
Week	Dose (per 250 mL bag)	Initial Infusion Rate	Subsequent Infusion Rate <sup>†</sup>
Week 1 (split dose infusion)			
Week 1 <i>Day 1</i>	350 mg	50 mL/hr	75 mL/hr
Week 1 <i>Day 2</i>	700 mg	50 mL/hr	75 mL/hr
Week 2	1050 mg	85 mL/hr	
Subsequent weeks*	1050 mg	125 mL/hr	
1400 mg Dose			
Week	Dose (per 250 mL bag)	Initial Infusion Rate	Subsequent Infusion Rate
Week 1 (split dose infusion)			
Week 1 <i>Day 1</i>	350 mg	50 mL/hr	75 mL/hr
Week 1 <i>Day 2</i>	1050 mg	35 mL/hr	50 mL/hr
Week 2	1400 mg	65 mL/hr	
Week 3	1400 mg	85 mL/hr	
Subsequent weeks*	1400 mg	125 mL/hr	

<sup>\*</sup> After Week 5, patients are dosed every 2 weeks.

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

### Missed dose(s)

If a planned dose of RYBREVANT® is missed, the dose should be administered as soon as possible and the dosing schedule should be adjusted accordingly, maintaining the treatment interval.

### Dose modifications

The recommended dose reductions for adverse reactions (see Table 6) are listed in Table 5.

**Table 5: RYBREVANT® Dose Reductions for Adverse Reactions**

<b>Body Weight at Baseline</b>	<b>Initial Dose</b>	<b>1<sup>st</sup> Dose Reduction</b>	<b>2<sup>nd</sup> Dose Reduction</b>	<b>3<sup>rd</sup> Dose Modification</b>
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	

The recommended dosage modifications for adverse reactions are provided in Table 6.

**Table 6: RYBREVANT® Dosage Modifications for Adverse Reactions**

<b><u>Adverse Reaction</u></b>	<b><u>Severity</u></b>	<b><u>Dose Modification</u></b>
<b><u>Infusion-Related Reactions (IRR)</u></b> (see <i>Warnings and Precautions</i> )	Grade 1 to 3	<ul style="list-style-type: none"> <li>• Interrupt infusion at the first sign of IRRs.</li> <li>• Additional supportive medications (e.g., additional glucocorticoids, antihistamine, antipyretics and antiemetics) should be administered as clinically indicated.</li> <li>• Upon resolution of symptoms, resume infusion at 50% of the previous rate.</li> <li>• If there are no additional symptoms, the rate may be increased per the recommended infusion rate (see Table 4).</li> <li>• Pre-medications should be administered prior to the next dose.</li> </ul>
	Recurrent Grade 3 or Grade 4	Permanently discontinue.
<b><u>Interstitial Lung Disease / Pneumonitis</u></b> (see <i>Warnings and Precautions</i> )	Suspected ILD/ pneumonitis	Withhold.
	Confirmed ILD/ pneumonitis	Permanently discontinue.
<b><u>Skin and Nail Reactions</u></b> (see <i>Warnings and Precautions</i> )	Grade 2	<ul style="list-style-type: none"> <li>• Supportive care should be initiated.</li> <li>• If there is no improvement after 2 weeks, consider reducing the dose (see Table 5).</li> </ul>
	Grade 3	<ul style="list-style-type: none"> <li>• Supportive care should be initiated.</li> <li>• Withhold until the adverse reaction improves to ≤ Grade 2</li> <li>Resume at reduced dose (see Table 5).</li> </ul>
	Grade 4 (including severe bullous, blistering or exfoliating skin conditions)	Permanently discontinue.
<b><u>Other Adverse Reactions</u></b> (see <i>Adverse Reactions</i> )	Grade 3	<ul style="list-style-type: none"> <li>• Withhold until adverse reaction improves to ≤ Grade 1 or baseline.</li> <li>• Resume at same dose if recovery occurs within 1 week.</li> <li>• Resume at reduced dose (see Table 5) if recovery occurs after 1 week.</li> <li>• Consider permanently discontinuing if recovery does not occur within 4 weeks.</li> </ul>
	Grade 4	<ul style="list-style-type: none"> <li>• Withhold until adverse reaction improves to ≤ Grade 1 or baseline.</li> </ul>

		<ul style="list-style-type: none"> <li>• Resume at reduced dose (see Table 5) if recovery occurs within 4 weeks.</li> <li>• Consider permanently discontinuing if recovery does not occur within 4 weeks.</li> </ul>
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## Special populations

### ***Pediatrics (17 years of age and younger)***

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

### ***Elderly (65 years of age and older)***

Of the 380 patients treated with RYBREVANT® in EDI1001, 41% were 65 years of age or older, and 11% were 75 years of age or older. No overall differences in safety or effectiveness were observed between patients ≥ 65 years of age and patients < 65 years of age. No dosage adjustment is necessary (see *Pharmacokinetic Properties*).

### ***Renal impairment***

No formal studies of amivantamab in patients with renal impairment have been conducted. Based on population pharmacokinetic (PK) analyses, no dosage adjustment is necessary for patients with mild or moderate renal impairment. No data are available in patients with severe renal impairment (see *Pharmacokinetic Properties*).

### ***Hepatic impairment***

No formal studies of amivantamab in patients with hepatic impairment have been conducted. Based on population PK analyses, no dosage adjustment is necessary for patients with mild hepatic impairment. No data are available in patients with moderate or severe hepatic impairment (see *Pharmacokinetic Properties*).

## Administration

### ***Preparation for administration***

RYBREVANT® solution must be diluted and prepared for intravenous infusion by a healthcare professional using aseptic technique.

1. Determine the dose required (either 1050 mg or 1400 mg) and number of RYBREVANT® vials needed based on patient's baseline weight (see *Dosage*). Each vial of RYBREVANT® contains 350 mg of amivantamab.
2. Check that the RYBREVANT® solution is colorless to pale yellow. Do not use if discoloration or visible particles are present.
3. Withdraw and then discard a volume of either 5% dextrose [glucose] 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). Infusion bags must be made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE), or polyolefin blend (PP+PE).

4. Withdraw 7 mL of RYBREVANT<sup>®</sup> from each vial and add it to the infusion bag. The final volume in the infusion bag should be 250 mL. Each vial contains a 0.5 mL overflow to ensure sufficient extractable volume. Discard any unused portion left in the vial.
5. Gently invert the bag to mix the solution. Do not shake.
6. Visually inspect the diluted solution before administration. Do not use if discoloration or visible particles are observed.
7. Diluted solutions should be administered within 10 hours (including infusion time) at room temperature (15°C to 25°C) and in room light.

### **Administration**

1. 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). Administration sets must be made of either polyurethane (PU), polybutadiene (PBD), PVC, PP, or PE.
2. Do not infuse RYBREVANT<sup>®</sup> concomitantly in the same intravenous line with other agents.
3. This medicinal product is for single use only. Any unused medicinal product should be disposed of in accordance with local requirements.

### **Contraindications**

Hypersensitivity to the active substance(s) or to any of the excipients listed in *List of Excipients*.

### **Warnings and Precautions**

The data described in the WARNINGS AND PRECAUTIONS reflects the safety profile of 380 patients with locally advanced or metastatic NSCLC who received 1050 mg (for patients < 80 kg) or 1400 mg (for patients ≥ 80 kg) of RYBREVANT<sup>®</sup> monotherapy in Study EDI1001.

#### **Infusion-related reactions**

Infusion-related reactions occurred in 67% of patients treated with RYBREVANT<sup>®</sup>. Ninety-eight percent of IRRs were Grade 1-2. Ninety-nine percent of IRRs occurred at the first infusion with a median time to onset of 60 minutes. The most frequent signs and symptoms include chills, nausea, dyspnea, flushing, chest discomfort, and vomiting.

Prior to initial infusion (Week 1) of RYBREVANT<sup>®</sup>, administer antihistamines, antipyretics, and glucocorticoids to reduce the risk of IRRs. For subsequent doses, administer antihistamines and antipyretics. Administer the initial infusion of RYBREVANT<sup>®</sup> in split doses on Week 1, Days 1 and 2 (see *Dosage and Administration*).

Treat patients with RYBREVANT<sup>®</sup> in a setting with appropriate medical support necessary to treat IRRs. Interrupt RYBREVANT<sup>®</sup> infusion at the first sign of IRRs and institute post-infusion medication as clinically indicated. Upon resolution of symptoms, resume the infusion at 50% of the previous rate. For recurrent Grade 3 or 4 IRRs, permanently discontinue RYBREVANT<sup>®</sup> (see *Dosage and Administration*).

## **Interstitial lung disease**

Interstitial lung disease (ILD) or ILD-like adverse reactions (e.g. pneumonitis) occurred in 2.6% of patients treated with RYBREVANT<sup>®</sup>. Patients with a medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD have not been studied.

Monitor patients for symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). If symptoms develop, interrupt treatment with RYBREVANT<sup>®</sup> pending investigation of these symptoms. Evaluate suspected ILD and initiate appropriate treatment as necessary. Discontinue RYBREVANT<sup>®</sup> in patients with confirmed ILD (see *Dosage and Administration*).

## **Skin and nail reactions**

Rash (including dermatitis acneiform), pruritis and dry skin occurred in 76% of patients treated with RYBREVANT<sup>®</sup>. Most cases were Grade 1 or 2, with Grade 3 events occurring in 3% of patients. Rash leading to RYBREVANT<sup>®</sup> discontinuation occurred in 0.3% of patients. Rash usually developed within the first 4 weeks of therapy, with a median time to onset of 14 days. Nail toxicity occurred in patients treated with RYBREVANT<sup>®</sup>. Most events were Grade 1 or 2, with Grade 3 nail toxicity occurring in 1.8% of patients.

Toxic epidermal necrolysis (TEN) has been reported. Permanently discontinue RYBREVANT<sup>®</sup> if TEN is confirmed.

Instruct patients to limit sun exposure during and for 2 months after RYBREVANT<sup>®</sup> therapy. Protective clothing and use of sunscreen is advisable. Alcohol-free emollient cream is recommended for dry areas with the use of RYBREVANT<sup>®</sup>. If skin or nail reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 or poorly-tolerated Grade 2 events, add systemic antibiotics and oral steroids and consider dermatologic consultation. Withhold, dose reduce, or permanently discontinue RYBREVANT<sup>®</sup> based on severity (see *Dosage and Administration*).

## **Eye disorders**

Eye disorders, including keratitis (0.5%), occurred in 9% of patients treated with RYBREVANT<sup>®</sup>. Other reported adverse reactions included dry eye, blurred vision, eye pruritus, visual impairment, aberrant eyelash growth, ocular hyperemia, conjunctival hyperemia, blepharitis and uveitis. All events were Grade 1-2. Refer patients presenting with worsening eye symptoms promptly to an ophthalmologist and advise discontinuation of contact lenses until symptoms are evaluated.

## **Interactions**

No drug interaction studies have been performed.

## **Pregnancy, Breast-feeding and Fertility**

### **Pregnancy**

There are no human or animal data to assess the risk of RYBREVANT<sup>®</sup> in pregnancy. Administration of other EGFR and MET inhibitor molecules to pregnant animals has resulted in an increased incidence of impairment of embryo-fetal development, embryoletality, and abortion. Therefore, based on its mechanism of action and findings in animal models, RYBREVANT<sup>®</sup> could cause fetal harm when administered to a pregnant woman.

RYBREVANT<sup>®</sup> should not be used during pregnancy unless the benefit of treatment to the woman is considered to outweigh potential risks to the fetus. If the patient becomes pregnant while taking this drug, the patient should be informed of the potential risk to the fetus.

### **Breast-feeding**

It is not known whether RYBREVANT<sup>®</sup> is excreted in human or animal milk or affects milk production. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from amivantamab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Because of the potential for serious adverse reactions from RYBREVANT<sup>®</sup> in breast-fed infants, advise women not to breast-feed during treatment with RYBREVANT<sup>®</sup> and for 3 months following the last dose of RYBREVANT<sup>®</sup>.

### **Contraception**

Due to the risk that RYBREVANT<sup>®</sup> can cause fetal harm when administered to pregnant women, advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of RYBREVANT<sup>®</sup>. Male patients must use effective contraception (e.g., condom) and not donate or store semen during treatment and for 3 months after the last dose of RYBREVANT<sup>®</sup>.

### **Fertility**

No data are available to determine potential effects of RYBREVANT<sup>®</sup> on fertility in males or females.

## **Effects on Ability to Drive and Use Machines**

No studies on the effects on the ability to drive and use machines have been performed. If patients experience treatment-related symptoms affecting their ability to concentrate and react, it is recommended that they do not drive or use machines until the effect subsides.

## **Adverse Reactions**

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of amivantamab based on the comprehensive assessment of the available adverse event information. A causal relationship with amivantamab cannot be reliably established in individual cases. Further, 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 clinical practice.

The safety of RYBREVANT<sup>®</sup> was evaluated in Study EDI1001, which included 380 patients with locally advanced or metastatic NSCLC after failure of platinum-based chemotherapy. Patients received RYBREVANT<sup>®</sup> 1050 mg (for patients < 80 kg) or 1400 mg (for patients ≥ 80 kg) by intravenous infusion once weekly for 4 weeks, then every 2 weeks starting at Week 5 until disease progression or unacceptable toxicity. The median treatment duration was 4.1 months (range: 0.0 to 39.7 months).

The most frequent adverse reactions ≥ 20% were rash, IRR, nail toxicity, hypoalbuminemia, edema, fatigue, stomatitis, nausea, and constipation. Serious adverse reactions in > 1% of patients included ILD, IRR, and rash. Three percent of patients discontinued RYBREVANT<sup>®</sup> due to adverse reactions. The most frequent adverse reactions leading to treatment discontinuation were IRR, ILD, and nail toxicity.

Table 7 presents adverse reactions reported in patients treated with RYBREVANT<sup>®</sup> in Study EDI1001.

Adverse reactions observed during clinical studies are listed below by frequency category. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (frequency cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

**Table 7: Adverse reactions in Patients with NSCLC with Exon 20 Insertion Mutations in Study EDI1001 Treated with RYBREVANT<sup>®</sup> (N=380)**

System Organ Class Adverse Reaction	Frequency (all grades)	All Grades (%)	Grade 3-4 (%)
<b>Skin and subcutaneous tissue disorders</b>			
Rash <sup>a</sup>	Very common	76	3
Nail toxicity <sup>b</sup>	Very common	47	2
Dry skin <sup>c</sup>	Very common	19	0
Pruritus	Very common	18	0
Toxic epidermal necrolysis	Uncommon	0.3	0.3
<b>Injury, poisoning and procedural complications</b>			
Infusion-related reaction	Very common	67	2
<b>Gastrointestinal disorders</b>			
Stomatitis <sup>d</sup>	Very common	24	0.5
Nausea	Very common	23	0.5
Constipation	Very common	23	0
Vomiting	Very common	12	0.5
Diarrhea	Very common	11	2
Abdominal pain <sup>e</sup>	Common	9	0.8
<b>Metabolism and nutrition disorders</b>			
Hypoalbuminemia <sup>f</sup>	Very common	31	2

<b>System Organ Class Adverse Reaction</b>	<b>Frequency (all grades)</b>	<b>All Grades (%)</b>	<b>Grade 3-4 (%)</b>
Decreased appetite	Very common	16	0.5
Hypocalcemia	Very common	10	0.3
Hypokalemia	Common	9	2
Hypomagnesemia	Common	8	0
<b>General disorders and administration site conditions</b>			
Edema <sup>g</sup>	Very common	26	0.8
Fatigue <sup>h</sup>	Very common	26	0.8
<b>Investigations</b>			
Alanine aminotransferase increased	Very common	15	2
Aspartate aminotransferase increased	Very common	13	1
Blood alkaline phosphatase increased	Very common	12	0.5
<b>Nervous system disorders</b>			
Dizziness <sup>i</sup>	Very common	13	0.3
<b>Musculoskeletal and connective tissue disorders</b>			
Myalgia	Very common	11	0.3
<b>Eye disorders</b>			
Other eye disorders <sup>j</sup>	Common	6	0
Visual impairment <sup>k</sup>	Common	3	0
Growth of eyelashes <sup>l</sup>	Common	1	0
Keratitis	Uncommon	0.5	0
Uveitis	Uncommon	0.3	0
<b>Respiratory, thoracic and mediastinal disorders</b>			
Interstitial lung disease <sup>m</sup>	Common	3	0.5

<sup>a</sup> Rash: acne, dermatitis, dermatitis acneiform, erythema, erythema multiforme, folliculitis, impetigo, palmar-plantar erythrodysesthesia syndrome, perineal rash, perioral dermatitis, pustule, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin lesion

<sup>b</sup> Nail toxicity: ingrowing nail, nail bed infection, nail cuticle fissure, nail disorder, nail ridging, onychoclasia, onycholysis, paronychia

<sup>c</sup> Dry skin: dry skin, eczema, eczema asteatotic, skin fissures, xeroderma

<sup>d</sup> Stomatitis: aphthous ulcer, cheilitis, glossitis, lip ulceration, mouth ulceration, mucosal inflammation, stomatitis

<sup>e</sup> Abdominal pain: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, epigastric discomfort, gastrointestinal pain

<sup>f</sup> Hypoalbuminaemia: blood albumin decreased, hypoalbuminemia

<sup>g</sup> Edema: eye edema, eyelid edema, face edema, generalized edema, localized edema, edema, edema peripheral, periorbital edema, peripheral swelling, swelling face

<sup>h</sup> Fatigue: asthenia, fatigue

<sup>i</sup> Dizziness: dizziness, dizziness exertional, vertigo

<sup>j</sup> Other eye disorders: blepharitis, conjunctival hyperemia, corneal irritation, dry eye, episcleritis, eye disorder, eye pruritus, noninfective conjunctivitis, ocular hyperemia

<sup>k</sup> Visual impairment: vision blurred, visual acuity reduced, visual impairment

<sup>l</sup> Growth of eyelashes: growth of eyelashes, trichomegaly

<sup>m</sup> Interstitial lung disease: interstitial lung disease, pneumonitis

## **Overdose**

### **Symptoms and signs**

There is no information on overdosage with RYBREVANT®.

### **Treatment**

There is no known specific antidote for RYBREVANT® overdose. In the event of an overdose, stop RYBREVANT®, undertake general supportive measures until clinical toxicity has diminished or resolved.

## **PHARMACOLOGICAL PROPERTIES**

### **Pharmacodynamic Properties**

Pharmacotherapeutic group: EGFR and MET inhibitor, ATC code: L01FX18

#### **Mechanism of action**

Amivantamab is a low-fucose, fully-human IgG1-based EGFR-MET bispecific antibody with immune cell-directing activity that targets tumors with activating and resistance EGFR mutations and MET mutations and amplifications. Amivantamab binds to the extracellular domains of EGFR and MET.

Preclinical studies show amivantamab is active against tumors with primary EGFR activating mutations such as Exon 19 deletions, L858R substitution, and Exon 20 insertion mutations; secondary EGFR resistance mutations such as T790M and C797S; and resistance to EGFR inhibition due to activation of the MET pathway. Amivantamab disrupts EGFR and MET signaling functions through blocking ligand binding and enhancing degradation of EGFR and MET, thereby preventing tumor growth and progression. 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.

#### **Pharmacodynamic effects**

##### ***Albumin***

Amivantamab decreased serum albumin concentration, a pharmacodynamic effect of MET inhibition, typically during the first 8 weeks; thereafter, albumin concentration stabilized for the remainder of amivantamab treatment.

##### ***Immunogenicity***

As with all therapeutic proteins, there is the potential for immunogenicity. In a clinical trial of patients with locally advanced or metastatic NSCLC treated with RYBREVANT®, 3 (1%) of the 286 evaluable patients tested positive for anti-amivantamab antibodies.

## Clinical studies

### ***Locally advanced or metastatic NSCLC with exon 20 insertion mutations***

EDI1001 (CHRYSLIS) is a multicenter, open-label, multi-cohort study conducted to assess the safety and efficacy of RYBREVANT® in subjects with locally advanced or metastatic NSCLC. Efficacy was evaluated in 114 subjects with locally advanced or metastatic NSCLC who had EGFR Exon 20 insertion mutations as determined by previous local standard of care testing, whose disease had progressed on or after platinum-based chemotherapy, and who had median follow-up of 12.5 months. RYBREVANT® was administered intravenously at 1050 mg for subjects < 80 kg or 1400 mg for subjects ≥ 80 kg once weekly for 4 weeks, then every 2 weeks starting at Week 5 until disease progression or unacceptable toxicity.

The median age was 62 (range: 36–84) years, with 41% of the patients ≥ 65 years of age; 61% were female; and 52% were Asian and 37% were White. The median number of prior therapies was 2 (range: 1 to 7 therapies). At baseline, 29% had Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 70% had ECOG performance status of 1; 57% never smoked; 100% had Stage IV cancer; and 25% had previous treatment for brain metastases. Insertions in Exon 20 were observed at 8 different residues; the most common residues were A767 (22%), S768 (16%), D770 (12%), and N771 (11%).

Efficacy results are summarized in Table 8.

**Table 8: Efficacy Results for EDI1001 (CHRYSLIS)**

	<b>BICR Assessment (N=114)</b>	<b>Investigator Assessment (N=114)</b>
<b>Overall Response Rate<sup>a,b</sup> (95% CI)</b>	43% (34%, 53%)	37% (28%, 46%)
Complete response	3%	0%
Partial response	40%	37%
<b>Clinical Benefit Rate<sup>a,c</sup> (95% CI)</b>	74% (65%, 82%)	75% (67%, 83%)
<b>Duration of Response<sup>a</sup> (DOR)</b>		
Median (95% CI), months <sup>d</sup>	10.8 (6.9, 15.0)	12.5 (6.5, 16.1)
Patients with DOR ≥ 6 months	55%	64%
<b>Median Progression-Free Survival<sup>a</sup> (95% CI), months</b>	6.7 (5.5, 9.7)	6.9 (5.6, 8.6)
<b>Median Time to Treatment Failure (95% CI), months</b>	8.1 (6.7, 10.6)	
<b>Median Overall Survival (95% CI), months</b>	22.8 (17.5, NE)	

BICR=Blinded Independent Central Review; NE=Not Estimable

- <sup>a</sup> by RECIST v1.1
- <sup>b</sup> Confirmed response.
- <sup>c</sup> Clinical benefit rate is defined as complete response + partial response + stable disease (duration of at least 11 weeks).
- <sup>d</sup> Based on Kaplan-Meier estimate

Anti-tumor activity was observed across studied mutation subtypes.

## Pharmacokinetic Properties

Amivantamab area under the concentration-time curve ( $AUC_{1\text{week}}$ ) increases proportionally over a dose range from 350 to 1750 mg (0.33 to 1.67 times the recommended dose for subjects < 80 kg and 0.25 to 1.25 times the recommended dose for subjects  $\geq$  80 kg).

Following administration of RYBREVANT<sup>®</sup> at the recommended dose and schedule, the mean  $\pm$  SD serum maximal concentration ( $C_{\text{max}}$ ) was  $836 \pm 264$  mcg/mL at 1050 mg for subjects < 80 kg and  $655 \pm 109$  mcg/mL at 1400 mg for subjects  $\geq$  80 kg at the end of weekly dosing following the fifth dose. The mean  $\pm$  SD  $AUC_{1\text{week}}$  following the fifth dose was  $94,946 \pm 35,440$  mcg.h/mL at 1050 mg for subjects < 80 kg and  $76,946 \pm 14,557$  mcg.h/mL at 1400 mg for subjects  $\geq$  80 kg. The mean serum  $AUC_{1\text{week}}$  was approximately 2.9-fold higher after the fifth dose following the weekly dosing compared to the first dose.

When RYBREVANT<sup>®</sup> was administered, amivantamab steady state was achieved approximately 2 months into the every 2-week dosing period (by the ninth infusion) at 1050 mg, and amivantamab mean  $\pm$  SD ratio of  $AUC_{1\text{week}}$  at steady state to  $AUC_{1\text{week}}$  after the first dose was  $2.44 \pm 0.54$ .

## Distribution

Amivantamab mean  $\pm$  SD volume of distribution estimated from population PK parameters was  $5.13 \pm 1.78$  L following administration of the recommended dose of RYBREVANT<sup>®</sup>.

## Elimination

Amivantamab clearance decreased with increasing dose and with multiple dosing. The mean  $\pm$  SD linear clearance was estimated to be  $360 \pm 144$  mL/day and the mean  $\pm$  SD estimated terminal half-life associated with linear clearance estimated from population PK parameter estimates was  $11.3 \pm 4.53$  days following administration of the recommended dose of RYBREVANT<sup>®</sup>.

## Special populations

### ***Pediatrics (17 years of age and younger)***

The pharmacokinetics of RYBREVANT<sup>®</sup> in pediatric patients have not been investigated.

### ***Elderly (65 years of age and older)***

No clinically meaningful differences in the pharmacokinetics of amivantamab were observed based on age (32-87 years).

### ***Renal impairment***

No clinically meaningful effect on the pharmacokinetics of amivantamab was observed in patients with mild ( $60 \leq$  creatinine clearance [CrCl]  $< 90$  mL/min) and moderate ( $29 \leq$  CrCl  $< 60$  mL/min) renal impairment. The effect of severe renal impairment ( $15 \leq$  CrCl  $< 29$  mL/min) on amivantamab pharmacokinetics is unknown.

### ***Hepatic impairment***

Changes in hepatic function are unlikely to have any effect on the elimination of amivantamab since IgG1-based molecules such as amivantamab are not metabolized through hepatic pathways.

No clinically meaningful effect in the pharmacokinetics of amivantamab was observed based on mild hepatic impairment [(total bilirubin  $\leq$  ULN and AST  $>$  ULN) or (ULN  $<$  total bilirubin  $\leq 1.5 \times$  ULN)]. The effect of moderate (total bilirubin 1.5 to 3 times ULN) and severe (total bilirubin  $>$  3 times ULN) hepatic impairment on amivantamab pharmacokinetics is unknown.

### ***Gender***

The clearance of amivantamab was 24% higher in males than in females; however, no clinically meaningful differences in the pharmacokinetics of amivantamab were observed based on gender.

### ***Weight***

The central volume of distribution and clearance of amivantamab increased with increasing body weight. Similar amivantamab exposures were achieved at the recommended dose of RYBREVANT® in patients with a body weight  $< 80$  kg who received 1050 mg and patients with a body weight  $\geq 80$  kg who received 1400 mg.

## **NON-CLINICAL INFORMATION**

In repeat-dose toxicity studies in cynomolgus monkeys, amivantamab was well-tolerated at weekly doses up to 120 mg/kg intravenously for 6 weeks or 3 months ( $\sim 6$ - $8 \times C_{\max}$  and  $\sim 5$ - $7 \times$  AUC human exposure for 1050 and 1400 mg intravenous doses). There were no effects on cardiovascular, respiratory, and nervous system function. Clinical pathology demonstrated non-adverse elevations in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and globulins, and non-adverse decreases in albumin when compared to the control group. All these values returned to normal ranges in recovery groups. A subcutaneous local tolerance study showed that amivantamab was well tolerated at injection sites in cynomolgus monkeys administered two 125 mg/kg weekly doses.

### **Carcinogenicity and Mutagenicity**

No animal studies have been performed to establish the carcinogenic potential of amivantamab. Routine genotoxicity and carcinogenicity studies are generally not applicable to biologic pharmaceuticals as large proteins cannot diffuse into cells and cannot interact with DNA or chromosomal material.

## Reproductive Toxicology

No reproductive toxicology studies have been performed to evaluate the potential effects of amivantamab.

## PHARMACEUTICAL INFORMATION

### List of Excipients

EDTA disodium salt dihydrate

L-Histidine

L-Histidine hydrochloride monohydrate

L-Methionine

Polysorbate 80

Sucrose

Water for Injection

### Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in *Dosage and Administration*.

### Shelf Life

Unopened vials:

See expiry date on the outer pack.

After dilution:

Since amivantamab solutions do not contain a preservative, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used immediately. Administer diluted solutions within 10 hours (including infusion time) at room temperature (15°C to 25°C) and in room light.

### Storage Conditions

Store in a refrigerator at 2°C to 8°C.

Do not freeze.

Store in the original package in order to protect from light.

For storage conditions after dilution of the medicinal product, see Shelf-Life.

Keep out of the sight and reach of children.

## **Nature and Contents of Container**

RYBREVANT® is available in cartons containing 1 single-use vial.

## **Instructions for Use and Handling and Disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **BATCH RELEASER**

Cilag AG  
Hochstrasse 201  
8200 Schaffhausen  
Switzerland

## **PRODUCT REGISTRANT**

Johnson & Johnson International (Singapore) Pte. Ltd.  
2 Science Park Drive  
#07-13, Ascent  
Singapore Science Park 1  
Singapore 118222

## **DATE OF REVISION OF TEXT**

29 November 2022 (CCDS 16 November 2021)