<u>เอกสารกำกับยาฉบับภาษาอังกฤษสำหรับแพทย์</u>

1. Name of the Medicinal Product

1.1 Product Name

RYBREVANT™ (INN: Amivantamab)

1.2 Strength

350 mg/7 mL (50 mg/mL)

1.3 Pharmaceutical Dosage Form

Injection

2. Qualitative and Quantitative Composition

2.1 Qualitative Declaration

Amivantamab is a low-fucose human immunoglobulin G1-based bispecific antibody directed against the EGF 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) injection for intravenous infusion is a sterile, preservative-free, colorless to pale yellow solution in single-dose vials. The pH is 5.7.

2.2 Quantitative Declaration

Each RYBREVANT vial contains 350 mg amivantamab (50mg/mL).

3. Pharmaceutical Form

Injection. colorless to pale yellow solution in a single-dose vial.

4. Clinical Particulars

4.1 Therapeutic indication

RYBREVANT (amivantamab) is 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 a validated 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 *[see Clinical Studies]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

4.2 Posology and method of administration

4.2.1 Patient Selection

Select patients for treatment with RYBREVANT based on the presence of EGFR exon 20 insertion mutations in tumor or plasma specimens *[see Clinical Studies].* If no mutation is detected in a plasma specimen, test tumor tissue.

4.2.2 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.

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

* 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 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

Administer premedications before each RYBREVANT infusion as recommended *[see Posology and Method of Administration (4.2.3)]*. 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 *[see Posology and Method of Administration (4.2.5), (4.2.6)].* Administer RYBREVANT until disease progression or unacceptable toxicity.

4.2.3 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: [see *Special Warnings and Precautions (4.4.1)*].

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 1,000 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.

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.

4.2.4 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	

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) *[see Special Warnings and Precautions (4.4.1)]*	Grade 1 to 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 (see Table 3).
	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.
Interstitial Lung Disease (ILD)/pneumonitis *[see Special Warnings and Precautions (4.4.2)].*	Any Grade	• Withhold RYBREVANT if ILD/pneumonitis is suspected. • Permanently discontinue RYBREVANT if ILD/pneumonitis is confirmed.
Dermatologic Adverse Reactions (including dermatitis acneiform, pruritus, dry skin) *[see Special Warnings and Precautions (4.4.3)]*	Grade 2	• Initiate supportive care management. • Reassess after 2 weeks; if rash does not improve, consider dose reduction.
	Grade 3	• Withhold RYBREVANT and initiate supportive care management. • Upon recovery to ≤ Grade 2, resume RYBREVANT at reduced dose. • 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 *[see Undesirable effects (4.8.1)]*	Grade 3	• Withhold RYBREVANT until recovery to ≤ Grade 1 or baseline. • Resume at the same dose if recovery occurs within 1 week. • Resume at reduced dose if recovery occurs after 1 week but within 4 weeks. • Permanently discontinue if recovery does not occur within 4 weeks.
	Grade 4	• Withhold RYBREVANT until recovery to ≤Grade 1 or baseline. • Resume at reduced dose if recovery occurs within 4 weeks.

		• Permanently discontinue if recovery does not occur within 4 weeks. • Permanently discontinue for recurrent Grade 4 reactions.

4.2.5 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 *[see Posology and Method of Administration (4.2.2)]*. Each vial of RYBREVANT contains 350 mg of amivantamab.
- 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).

4.2.6 Administration

Administer the diluted solution [*see Posology and Method of Administration (4.2.5)*] 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 *[see Special Warnings and Precautions (4.4.1)]*. 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 RYBREVANT infusion intravenously according to the infusion rates in Table 6.

Table 6: Infusion Rates for RYBREVANT Administration

1050 mg Dose			
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			
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.

4.2.3 Pediatric Use

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

4.2.4 Geriatric Use

Of the 129 patients treated with RYBREVANT, 41% were 65 years of age or older, and 9% were 75 years of age or older. No clinically important differences in safety or efficacy were observed between patients who were ≥65 years of age and younger patients.

4.3 Contraindication

None.

4.4 Special warnings and precautions

4.4.1 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.

Based on the safety population *[see Undesirable effects (4.8.1)],* 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 *[see Posology and Method of Administration (4.2.3)]*. Administer RYBREVANT via a peripheral line on Week 1 and Week 2 *[see Posology and Method of Administration (4.2.6)]*.

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 Posology and Method of Administration (4.2.4)]*.

4.4.2 Interstitial Lung Disease/Pneumonitis

RYBREVANT can cause interstitial lung disease (ILD)/pneumonitis. Based on the safety population *[see Undesirable effects (4.8.1)]*, 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 *[see Posology and Method of Administration (4.2.4)]*.

4.4.3 Dermatologic Adverse Reactions

RYBREVANT can cause rash (including dermatitis acneiform), pruritus and dry skin. Based on the safety population *[see Undesirable effects (4.8.1)]*, 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 *[see Undesirable effects (4.8.1)].*

Toxic epidermal necrolysis (TEN) 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 *[see Posology and Method of Administration (4.2.4)]*.

4.4.4 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 *[see Undesirable effects (4.8.1)],* 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 Posology and Method of Administration (4.2.4)]*.

4.4.5 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 inhibitor molecules to pregnant animals has resulted in an increased incidence of impairment of embryo-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 final dose of RYBREVANT. *[see Pregnancy and lactation (4.6.1, 4.6.3)]*.

4.5 Interaction with other medicinal products and other forms of interactions

No drug interaction studies have been performed.

4.6 Pregnancy and lactation

4.6.1 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 are 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 (*see Data*). Advise pregnant women of the potential risk to a fetus.

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 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 displayed defects in muscle development in multiple organs. Human IgG1 is known to cross the placenta; therefore, amivantamab has the potential to be transmitted from the mother to the developing fetus.

4.6.2 Lactation

Risk Summary

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

4.6.3 Females and Males of Reproductive Potential

RYBREVANT can cause fetal harm when administered to a pregnant woman *[see Pregnancy and lactation (4.6.1)].*

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiating RYBREVANT.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVANT.

4.7 Effect on ability to drive and use machine

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.

4.8 Undesirable effects

The following adverse reactions are discussed elsewhere in the labeling:

- Infusion-Related Reactions *[see Special Warnings and Precautions (4.4.1)]*
- Interstitial Lung Disease/Pneumonitis *[see Special Warnings and Precautions (4.4.2)]*
- Dermatologic Adverse Reactions *[see Special Warnings and Precautions (4.4.3)]*
- Ocular Toxicity *[see Special Warnings and Precautions (4.4.4)]*

4.8.1 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 safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to RYBREVANT as a single agent in the CHRYSALIS study in 302 patients with locally advanced or metastatic NSCLC who received a dose of 1050 mg (for patients <80 kg) or 1400 mg (for patients ≥80 kg) once weekly for 4 weeks, then every 2 weeks thereafter. Among 302 patients who received RYBREVANT, 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 decreased lymphocytes, decreased phosphate, decreased albumin, increased glucose, increased gamma glutamyl transferase, decreased sodium, decreased potassium, and increased alkaline phosphatase.

The data described below reflect exposure to RYBREVANT at the recommended dosage in 129 patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations whose disease had progressed on or after platinum-based chemotherapy. Among patients who received RYBREVANT, 44% were exposed for 6 months or longer and 12% were exposed for greater than one year.

The median age was 62 years (range: 36 to 84 years); 61% were female; 55% were Asian, 35% were White, and 2.3% were Black; and 82% had baseline body weight <80 kg.

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.

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 pneumonia, IRR, pneumonitis/ILD, dyspnea, pleural effusion, and rash.

Dose interruptions of RYBREVANT due to an adverse reaction occurred in 78% of patients. Infusion-related reactions (IRR) requiring infusion interruptions occurred in 59% of patients. Adverse reactions requiring dose interruption in ≥5% of patients included dyspnea, nausea, rash, vomiting, fatigue, and diarrhea.

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 7 summarizes the adverse reactions in CHRYSALIS.

Table 7: 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

Adverse Reactions	RYBREVANT (N=129)	
	All Grades (%)	Grades 3 or 4 (%)
Skin and subcutaneous tissue disorders		
Rash[a]	84	3.9
Pruritus	18	0
Dry skin	14	0
General disorders and administration site conditions		
Infusion related reaction	64	3.1
Fatigue[b]	33	2.3
Edema[c]	27	0.8
Pyrexia	13	0
Infections and infestations		
Paronychia	50	3.1
Pneumonia[d]	10	0.8
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[e]	47	0
Respiratory, thoracic and mediastinal disorders		
Dyspnea[f]	37	2.3
Cough[g]	25	0
Gastrointestinal disorders		
Nausea	36	0
Stomatitis[h]	26	0.8
Constipation	23	0
Vomiting	22	0
Diarrhea	16	3.1
Abdominal Pain[i]	11	0.8
Vascular disorders		
Hemorrhage[j]	19	0
Metabolism and nutrition disorders		
Decreased appetite	15	0
Nervous system disorders		
Peripheral neuropathy[k]	13	0
Dizziness	12	0.8
Headache[l]	10	0.8

[a] Rash: acne, dermatitis, dermatitis acneiform, eczema, eczema asteatotic, palmar-plantar erythrodysesthesia syndrome, perineal rash, rash, rash erythematous, rash maculo-papular, rash papular, rash vesicular, skin exfoliation, toxic epidermal necrolysis

[b] Fatigue: asthenia, fatigue

[c] Edema: eyelid edema, face edema, generalized edema, lip edema, edema, edema peripheral, periorbital edema, peripheral swelling

[d] Pneumonia: atypical pneumonia, lower respiratory tract infection, pneumonia, pneumonia aspiration, and pulmonary sepsis

[e] Musculoskeletal pain: arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain

[f] Dyspnea: dyspnea, dyspnea exertional

[g] Cough: cough, productive cough, upper airway cough syndrome

[h] Stomatitis: aphthous ulcer, cheilitis, glossitis, mouth ulceration, mucosal inflammation, pharyngeal inflammation, stomatitis

[i] Abdominal pain: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and epigastric discomfort

[j] Hemorrhage: epistaxis, gingival bleeding, hematuria, hemoptysis, hemorrhage, mouth hemorrhage, mucosal hemorrhage
[k] Peripheral neuropathy: hypoesthesia, neuralgia, paresthesia, peripheral sensory neuropathy
[l] Headache: headache, migraine

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

Table 8 summarizes the laboratory abnormalities in CHRYSALIS.

Table 8: 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

Laboratory Abnormality	RYBREVANT[+] (N=129)	
	All Grades (%)	Grades 3 or 4 (%)
Chemistry		
Decreased albumin	79	8
Increased glucose	56	4
Increased alkaline phosphatase	53	4.8
Increased creatinine	46	0
Increased alanine aminotransferase	38	1.6
Decreased phosphate	33	8
Increased aspartate aminotransferase	33	0
Decreased magnesium	27	0
Increased gamma-glutamyl transferase	27	4
Decreased sodium	27	4
Decreased potassium	26	6
Hematology		
Decreased lymphocytes	36	8

[+] 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.

4.8.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other amivantamab products may be misleading.

In CHRYSALIS, 3 of the 286 (1%) patients who were treated with RYBREVANT and evaluable for the presence of anti-drug antibodies (ADA), tested positive for treatment-emergent anti-amivantamab antibodies (one at 27 days, one at 59 days and one at 168 days after the first dose) with titers of 1:40 or less. There are insufficient data to evaluate the effect of ADA on the pharmacokinetics, safety, or efficacy of RYBREVANT.

CLINICAL STUDIES

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 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.

Efficacy results are summarized in Table 9.

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.
NE=Not Estimable, CI=confidence interval.

5. Pharmacological Properties

Mechanism of Action

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

In *in vitro* and *in vivo* studies amivantamab 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.

5.1 Pharmacodynamic Properties

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

5.2 Pharmacokinetic Properties

Amivantamab exposures increased proportionally over a dosage range from 350 to 1750 mg (0.25 to 1.25 times the maximum approved recommended dosage). Steady state of amivantamab concentrations was achieved by the 9th infusion. The accumulation ratio at steady state was 2.4.

Distribution

The amivantamab mean (± SD) volume of distribution is 5.13 (± 1.78) L.

Elimination

The mean (± SD) clearance of amivantamab is 360 (± 144) mL/day and the terminal half-life is 11.3 (± 4.53) days.

Specific Populations

No clinically meaningful differences in the pharmacokinetics of amivantamab were observed based on age (range: 32-87 years), sex, race, creatinine clearance (CLcr 29 to 276 mL/min), or mild hepatic impairment [(total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5 times ULN)]. The pharmacokinetics of amivantamab 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. Amivantamab 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 were comparable between patients who weighed < 80 kg and received 1050 mg dose and patients who weighed ≥ 80 kg and received 1400 mg.

5.3 Preclinical Safety Data

5.3.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to assess the potential of amivantamab for carcinogenicity or genotoxicity. Fertility studies have not been performed to evaluate the

potential effects of amivantamab. In 6-week and 3-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs.

6. Pharmaceutical Particulars

6.1 List of excipients

EDTA disodium salt dihydrate (0.14 mg), L-histidine (2.3 mg), L-histidine hydrochloride monohydrate (8.6 mg), L-methionine (7 mg), polysorbate 80 (4.2 mg), sucrose (595 mg), and water for injection, USP.

6.2 Incompatibilities

None.

6.3 Shelf life

See expiry date on the outer pack.

6.4 Special precautions for storage

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.

Keep out of reach of children.

6.5 Nature and contents of container

How Supplied

RYBREVANT™ (amivantamab) 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.

PATIENT COUNSELING INFORMATION

Advise the patient to read the approved patient labeling (Patient Information).

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 *[see Special Warnings and Precautions (4.4.1)]*.

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 *[see Special Warnings and Precautions (4.4.2)]*.

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 *[see Special Warnings and Precautions (4.4.3)]*. 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 *[see Special Warnings and Precautions (4.4.4)]*.

Paronychia

Advise patients of the risk of paronychia. Advise patients to contact their healthcare provider for signs or symptoms of paronychia *[see Undesirable effects (4.8.1)].*

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 *[see Special Warnings and Precautions (4.4.5), Pregnancy and lactation (4.6.1, 4.6.3)]*.

Lactation

Advise women not to breastfeed during treatment with RYBREVANT and for 3 months after the final dose *[see Pregnancy and lactation (4.6.2)]*.

7. Marketing Authorization Holder

See below.

8. Marketing Authorization Number and Date of Authorization

Product Name	**Manufactured by**	**Market Authorization Number**	**Date of Authorization**
RYBREVANT	Cilag AG Hochstrasse 201 8200 Schaffhausen Switzerland	1C 15287/65 (NBC)	30-Nov-2022

9. Date of revision of the text

25-Sep-2023 (USPI V Nov-2022)

Imported by

Janssen-Cilag Ltd.

Bangkok, Thailand

To report Suspected Adverse Reactions, please contact us at *aepqcjacth@its.jnj.com*

For any product information, please contact us at *medinfosea@its.jnj.com*

Warning according to the announcement from Ministry of Public Health

This medicinal product may cause serious harm. It must be used only under physician's supervision.