1. NAME OF THE MEDICINAL PRODUCT

RYBREVANT® 350 mg concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of concentrate for solution for infusion contains 50 mg amivantamab.
One 7 mL vial contains 350 mg of amivantamab.

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.

Excipient with known effect:
One mL of solution contains 0.6 mg of polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

The solution is colourless to pale yellow, with a pH of 5.7 and an osmolality of approximately 310 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RYBREVANT® is indicated:
- in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy with osimertinib monotherapy as the most recent line of treatment.
- in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations.

4.2 Posology and method of administration

Treatment with RYBREVANT® should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

RYBREVANT® should be administered by a healthcare professional with access to appropriate medical support to manage infusion-related reactions (IRRs) if they occur.

Before initiation of RYBREVANT® therapy, EGFR mutation status in tumour tissue or plasma specimens must be established using a validated test method. If no mutation is detected in a plasma specimen, tumour tissue should be tested if available in sufficient amount and quality due to the potential for false negative results using a plasma-test. Testing may be performed at any time from initial diagnosis until the initiation of therapy; testing does not need to be repeated once EGFR mutation status has been established (see section 5.1).

Posology

Premedications should be administered to reduce the risk of IRRs with RYBREVANT® (see below “Dose modifications” and “Recommended concomitant medicinal products”).

Every 3 weeks
The recommended dosages of RYBREVANT®, when used in combination with carboplatin and pemetrexed, is provided in Table 1 (see below “Infusion rates” and Table 4).

Table 1: Recommended dosage of RYBREVANT® every 3 weeks

Body weight at baseline[a]	RYBREVANT® dose	Schedule	Number of vials
Less than 80 kg	1400 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1	4
	1750 mg	Every 3 weeks starting at Week 7 onwards	5
Greater than or equal to 80 kg	1750 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1	5
	2100 mg	Every 3 weeks starting at Week 7 onwards	6

[a] Dose adjustments not required for subsequent body weight changes.

When used in combination with carboplatin and pemetrexed, RYBREVANT® should be administered after carboplatin and pemetrexed in the following order: pemetrexed, carboplatin and then RYBREVANT®. See section 5.1 and the manufacturer's prescribing information for dosing instructions for carboplatin and pemetrexed.

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

Missed dose
If a planned dose 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
Dosing should be interrupted for Grade 3 or 4 adverse reactions until the adverse reaction resolves to ≤ Grade 1 or baseline. If an interruption is 7 days or less, restart at the current dose. If an interruption is longer than 7 days, it is recommended restarting at a reduced dose as presented in Table 2. See also specific dose modifications for specific adverse reactions below Table 2.

Table 2: Recommended dose modifications for adverse reactions

Dose at which the adverse reaction occurred	Dose after 1st interruption for adverse reaction	Dose after 2nd interruption for adverse reaction	Dose after 3rd interruption for adverse reaction
1400 mg	1050 mg	700 mg	Discontinue RYBREVANT®
1750 mg	1400 mg	1050 mg	
2100 mg	1750 mg	1400 mg	

Infusion-related reactions
Infusion should be interrupted at the first sign of IRRs. Additional supportive medicinal products (e.g., additional glucocorticoids, antihistamine, antipyretics and antiemetics) should be administered as clinically indicated (see section 4.4).

- Grade 1-3 (mild-severe): Upon recovery of symptoms, resume infusion at 50% of the previous rate. If there are no additional symptoms, the rate may be increased per the recommended infusion rate (see Tables 5 and 6). Concomitant medicinal products should be administered at the next dose (including dexamethasone (20 mg) or equivalent (see Table 3).
- Recurrent Grade 3 or Grade 4 (life-threatening): Permanently discontinue RYBREVANT®.

Skin and nail reactions
If the patient develops a Grade 1-2 skin or nail reaction, supportive care should be initiated; if there is no improvement after 2 weeks, dose reduction should be considered for persistent Grade 2 rash (see Table 2). If the patient develops a Grade 3 skin or nail reaction, supportive care should be initiated, and interruption of RYBREVANT® should be considered until the adverse reaction improves. Upon recovery of the skin or nail reaction to ≤ Grade 2, RYBREVANT® should be resumed at a reduced dose. If the patient develops Grade 4 skin reactions, permanently discontinue RYBREVANT® (see section 4.4).

Interstitial lung disease

RYBREVANT® should be withheld if interstitial lung disease (ILD) or ILD-like adverse reactions (pneumonitis) is suspected. If the patient is confirmed to have ILD or ILD-like adverse reactions (e.g., pneumonitis), permanently discontinue RYBREVANT® (see section 4.4).

Recommended concomitant medicinal products

Prior to infusion (Week 1, Days 1 and 2), antihistamines, antipyretics, and glucocorticoids should be administered to reduce the risk of IRRs (see Table 3). For subsequent doses, antihistamines and antipyretics are required to be administered. Glucocorticoids should also be re-initiated after prolonged dose interruptions. Antiemetics should be administered as needed.

Table 3: Dosing schedule of premedications

Premedication	Dose	Route of administration	Recommended 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*	Paracetamol/Acetaminophen (650 to 1000 mg)	Intravenous	15 to 30 minutes
		Oral	30 to 60 minutes
Glucocorticoid‡	Dexamethasone (20 mg) or equivalent	Intravenous	60 to 120 minutes
Glucocorticoid+	Dexamethasone (10 mg) or equivalent	Intravenous	45 to 60 minutes

* Required at all doses.
‡ Required at initial dose (Week 1, Day 1) or at the next subsequent dose in the event of an IRR.
\+ Required at second dose (Week 1, Day 2); optional for subsequent doses.

Special populations

Paediatric population
There is no relevant use of amivantamab in the paediatric population in the treatment of non-small cell lung cancer.

Elderly
No dose adjustments are necessary (see section 4.8, section 5.1, and section 5.2).

Renal impairment
No formal studies of amivantamab in patients with renal impairment have been conducted. Based on population pharmacokinetic (PK) analyses, no dose adjustment is necessary for patients with mild or moderate renal impairment. Caution is required in patients with severe renal impairment as amivantamab has not been studied in this patient population (see section 5.2). If treatment is started, patients should be monitored for adverse reactions with dose modifications per the recommendations above.

Hepatic impairment
No formal studies of amivantamab in patients with hepatic impairment have been conducted. Based on population PK analyses, no dose adjustment is necessary for patients with mild hepatic impairment. Caution is required in patients with moderate or severe hepatic impairment as amivantamab has not been studied in this patient population (see section 5.2). If treatment is started, patients should be monitored for adverse reactions with dose modifications per the recommendations above.

Method of administration

RYBREVANT® is for intravenous use. It is administered as an intravenous infusion following dilution with sterile 5% glucose solution or sodium chloride 9 mg/mL (0.9%) solution for injection. RYBREVANT® must be administered with in-line filtration.

For instructions on dilution of the medicinal product before administration, see section 6.6.

Infusion rates
Following dilution, the infusion should be administered intravenously at the infusion rates presented in Table 4 or 6 below. Due to the frequency of IRRs at the first dose, amivantamab should be infused via a peripheral vein at Week 1 and Week 2; infusion via a central line may be administered for subsequent weeks when the risk of IRR

is lower (see section 6.6). It is recommended for the first dose to be prepared as close to administration as possible to maximise the likelihood of completing the infusion in the event of an IRR.

Table 4: Infusion rates for RYBREVANT® every 3 weeks

Body weight less than 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	33 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*	1750 mg	125 mL/hr	
Body weight greater than or equal to 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*	1400 mg	25 mL/hr	50 mL/hr
Week 2	1750 mg	65 mL/hr	
Week 3	1750 mg	85 mL/hr	
Week 4	1750 mg	125 mL/hr	
Subsequent weeks*	2100 mg	125 mL/hr	

* Starting at Week 7, patients are dosed every 3 weeks.

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

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infusion-related reactions

Infusion-related reactions commonly occurred in patients treated with amivantamab (see section 4.8).

Prior to initial infusion (Week 1), antihistamines, antipyretics, and glucocorticoids should be administered to reduce the risk of IRRs. For subsequent doses, antihistamines and antipyretics should be administered. The initial infusion should be administered in split doses on Week 1, Day 1 and 2.

Patients should be treated in a setting with appropriate medical support to treat IRRs. Infusions should be interrupted at the first sign of IRRs of any severity and post-infusion medicinal products should be administered as clinically indicated. Upon resolution of symptoms, the infusion should be resumed at 50% of the previous rate. For recurrent Grade 3 or Grade 4 IRRs, RYBREVANT® should be permanently discontinued (see section 4.2).

Interstitial lung disease

Interstitial lung disease (ILD) or ILD-like adverse reactions (e.g., pneumonitis) have been reported in patients treated with amivantamab (see section 4.8). Patients should be monitored for symptoms indicative of ILD/pneumonitis (e.g., dyspnoea, cough, fever). If symptoms develop, treatment with RYBREVANT® should be interrupted pending investigation of these symptoms. Suspected ILD or ILD-like adverse reactions should be evaluated and appropriate treatment should be initiated as necessary. RYBREVANT® should be permanently discontinued in patients with confirmed ILD or ILD-like adverse reactions (see section 4.2).

Skin and nail reactions

Rash (including dermatitis acneiform), pruritus, dry skin and skin ulcer occurred in patients treated with amivantamab (see section 4.8). Patients should be instructed to limit sun exposure during and for 2 months after RYBREVANT® therapy. Protective clothing and use of broad-spectrum UVA/UVB sunscreen are advisable. Alcohol-free emollient cream is recommended for dry areas. A prophylactic approach to rash prevention should be considered. If skin reactions develop, topical corticosteroids and topical and/or oral antibiotics should be administered. For Grade 3 or poorly-tolerated Grade 2 events, systemic antibiotics and oral steroids should also be administered. Patients presenting with severe rash that has an atypical appearance or distribution or lack improvement within 2 weeks should be referred promptly to a dermatologist. RYBREVANT® should be dose reduced, interrupted, or permanently discontinued based on severity (see section 4.2).

Toxic epidermal necrolysis (TEN) has been reported. Treatment with this medicinal product should be discontinued if TEN is confirmed.

Eye disorders
Eye disorders, including keratitis, occurred in patients treated with amivantamab (see section 4.8). Patients presenting with worsening eye symptoms should promptly be referred to an ophthalmologist and should discontinue use of contact lenses until symptoms are evaluated. For dose modifications for Grade 3 or 4 eye disorders, see section 4.2.

Sodium content
This medicinal product contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially "sodium-free". This medicinal product may be diluted in sodium chloride 9 mg/mL (0.9%) solution for infusion. This should be taken into consideration for patients on a controlled sodium diet (see section 6.6).

Polysorbate content
This medicinal product contains 0.6 mg of polysorbate 80 in each mL, which is equivalent to 4.2 mg per 7 mL vial. Polysorbates may cause hypersensitivity reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been performed. As an IgG1 monoclonal antibody, renal excretion and hepatic enzyme-mediated metabolism of intact amivantamab are unlikely to be major elimination routes. As such, variations in drug-metabolising enzymes are not expected to affect the elimination of amivantamab. Due to the high affinity to a unique epitope on EGFR and MET, amivantamab is not anticipated to alter drug-metabolising enzymes.

Vaccines
No clinical data are available on the efficacy and safety of vaccinations in patients taking amivantamab. Avoid the use of live or live-attenuated vaccines while patients are taking amivantamab.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/Contraception

Women of child-bearing potential should use effective contraception during and for 3 months after cessation of amivantamab treatment.

Pregnancy

There are no human data to assess the risk of amivantamab use during pregnancy. No animal reproductive studies were conducted to inform a drug-associated risk. Administration of EGFR and MET inhibitor molecules in pregnant animals resulted in an increased incidence of impairment of embryo-foetal development, embryo lethality, and abortion. Therefore, based on its mechanism of action and findings in animal models, amivantamab could cause foetal harm when administered to a pregnant woman. Amivantamab should not be given during pregnancy unless the benefit of treatment of the woman is considered to outweigh potential risks to the foetus. If the patient becomes pregnant while taking this medicinal product the patient should be informed of the potential risk to the foetus (see section 5.3).

Breast-feeding

It is unknown whether amivantamab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards. A risk to the breast-fed child cannot be excluded during this short period just after birth, although IgGs are likely to be degraded in the gastrointestinal tract of the breast-fed child and not absorbed. 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.

Fertility

There are no data on the effect of amivantamab on human fertility. Effects on male and female fertility have not been evaluated in animal studies.

4.7 Effects on ability to drive and use machines

RYBREVANT® may have moderate influence on the ability to drive and use machines. Please see section 4.8 (e.g., dizziness, fatigue, visual impairment). If patients experience treatment-related symptoms, including vision-related adverse reactions, 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

Summary of the safety profile

In the dataset of amivantamab in combination with carboplatin and pemetrexed (N=301), the most frequent adverse reactions in all grades were rash (83%), neutropenia (57%), nail toxicity (53%), infusion related reactions (51%), fatigue (43%), stomatitis (39%), nausea (43%), thrombocytopenia (40%), constipation (40%), oedema (40%), decreased appetite (33%), hypoalbuminaemia (32%), alanine aminotransferase increased (26%), aspartate aminotransferase increased (23%), vomiting (22%), and hypokalaemia (20%). Serious adverse reactions included rash (2.7%), venous thromboembolism (2.3%), thrombocytopenia (2.3%) and ILD (2.0%). Eight percent of patients discontinued RYBREVANT® due to adverse reactions. The most frequent adverse reactions leading to treatment discontinuation were IRR (2.7%), rash (2.3%), ILD (2.3%), and nail toxicity (1.0%).

Table 5 summarises the adverse drug reactions that occurred in patients receiving amivantamab in combination with chemotherapy.

The data reflects exposure to amivantamab in combination with carboplatin and pemetrexed in 301 patients with locally advanced or metastatic non-small cell lung cancer. Patients received amivantamab 1400 mg (for patients < 80 kg) or 1750 mg (for patients ≥ 80 kg) weekly for 4 weeks. Starting at Week 7, patients received amivantamab 1750 mg (for patients < 80 kg) or 2100 mg (for patients ≥ 80 kg) every 3 weeks. The median exposure to amivantamab in combination with carboplatin and pemetrexed was 7.7 months (range: 0.0 to 28.1 months).

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 (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); very rare (< 1/10000); 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 5: Adverse reactions in patients receiving amivantamab in combination with carboplatin and pemetrexed

System organ class Adverse reaction	**Frequency category**	**Any Grade (%)**	**Grade 3-4 (%)**
Blood and lymphatic system disorders			
Neutropenia	Very common	57	39
Thrombocytopenia		40	12
Metabolism and nutrition disorders			
Decreased appetite	Very common	33	1.3
Hypoalbuminaemia*		32	3.7
Hypokalaemia		20	6.6

Hypomagnesaemia		13	1.3
Hypocalcaemia		12	1.0
Nervous system disorders			
Dizziness*	Common	10	0.3
Vascular disorders			
Venous thromboembolism*	Very common	14	3.0
Eye disorders			
Other eye disorders*	Common	7.3	0
Visual impairment*		3.0	0
Growth of eyelashes	Uncommon	0.3	0
Keratitis		0.3	0
Uveitis		0.3	0
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease*	Common	2.3	1.7
Gastrointestinal disorders			
Nausea	Very common	43	1.0
Constipation		40	0.3
Stomatitis*		39	3.0
Vomiting		22	2.0
Diarrhoea		19	2.3
Abdominal pain*	Common	11	0.3
Haemorrhoids		9.3	0.7
Hepatobiliary disorders			
Alanine aminotransferase increased	Very common	26	4.3
Aspartate aminotransferase increased		23	0.7
Blood alkaline phosphatase increased	Common	10	0.3
Skin and subcutaneous tissue disorders			
Rash*	Very common	83	14
Nail toxicity*		53	4.3
Dry skin*		16	0
Pruritus		10	0
Skin ulcer	Common	3.7	0.7
Musculoskeletal and connective tissue disorders			
Myalgia	Common	5.0	0.7
General disorders and administration site conditions			
Fatigue*	Very common	43	4.7
Oedema*		40	1.3
Pyrexia		14	0
Injury, poisoning and procedural complications			
Infusion related reaction	Very common	51	3.0

* Grouped terms

Description of selected adverse reactions

Infusion-related reactions

In patients treated with amivantamab in combination with carboplatin and pemetrexed, infusion-related reactions occurred in 50% of patients. Greater than 94% of IRRs were Grade 1-2. A majority of IRRs occurred at the first infusion with a median time to onset of 60 minutes (range 0-7 hours), and the majority occurring within 2 hours of infusion start. Occasionally an IRR can occur at re-initiation of amivantamab after prolonged dose interruptions of more than 6 weeks.

Interstitial lung disease

Interstitial lung disease or ILD-like adverse reactions have been reported with the use of amivantamab as well as with other EGFR inhibitors. Interstitial lung disease or pneumonitis was reported in 2.3 % of patients treated with amivantamab in combination with carboplatin and pemetrexed. Patients with a medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD were excluded from the clinical study (see section 4.4).

Skin and nail reactions
Rash (including dermatitis acneiform), occurred in 83% of patients treated with amivantamab in combination with carboplatin and pemetrexed. Most cases were Grade 1 or 2, with Grade 3 rash events occurring in 14% of patients. Rash leading to amivantamab discontinuation occurred in 2.3% 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 amivantamab in combination with carboplatin and pemetrexed. Most events were Grade 1 or 2, with Grade 3 nail toxicity occurring in 4.3% of patients (see section 4.4).

Eye disorders
Eye disorders, including keratitis (0.3%), occurred in 11% of patients treated with amivantamab in combination with carboplatin and pemetrexed. Other reported adverse reactions included growth of eyelashes, visual impairment, uveitis, and other eye disorders. All events were Grade 1-2 (see section 4.4).

Special populations

Elderly
There are limited clinical data with amivantamab in patients 75 years of age or over (see section 5.1). No overall differences in safety were observed between patients ≥ 65 years of age and patients < 65 years of age.

Immunogenicity
As with all therapeutic proteins, there is the potential for immunogenicity. In clinical studies of patients with locally advanced or metastatic NSCLC treated with amivantamab, 4 of the 865 (0.5%) participants who were treated with RYBREVANT® and evaluable for the presence of anti-drug antibodies (ADA), tested positive for treatment-emergent anti-amivantamab antibodies. There was no evidence of an altered pharmacokinetic, efficacy, or safety profile due to anti-amivantamab antibodies.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to:

Pusat Farmakovigilans
Direktorat Pengawasan Keamanan, Mutu dan Ekspor Impor Obat Narkotika, Psikotropika, Prekursor, dan Zat Adiktif Badan Pengawas Obat dan Makanan Republik Indonesia
Address: Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Website: https://e-meso.pom.go.id/

4.9 Overdose

No maximum tolerated dose has been determined in a clinical study in which patients received up to 2100 mg administered intravenously. There is no known specific antidote for amivantamab overdose. In the event of an overdose, treatment with RYBREVANT® should be stopped, the patient should be monitored for any signs or symptoms of adverse events and appropriate general supportive measures should be instituted immediately until clinical toxicity has diminished or resolved.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Monoclonal antibodies and antibody drug conjugates, 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 tumours with activating EGFR mutations such as Exon 19 deletions, L858R substitution, and Exon 20 insertion mutations. Amivantamab binds to the extracellular domains of EGFR and MET.

Amivantamab disrupts EGFR and MET signalling functions through blocking ligand binding and enhancing degradation of EGFR and MET, thereby preventing tumour growth and progression. The presence of EGFR and MET on the surface of tumour 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 (see section 4.8); thereafter, albumin concentration stabilised for the remainder of amivantamab treatment.

Clinical efficacy and safety

Previously treated NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations (MARIPOSA-2)
MARIPOSA-2 is a randomised (2:2:1) open-label, multicentre Phase 3 study in patients with locally advanced or metastatic NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations (mutation testing could have been performed at or after the time of locally advanced or metastatic disease diagnosis. Testing did not need to be repeated at the time of study entry once EGFR mutation status was previously established) after failure of prior therapy including a third-generation EGFR tyrosine kinase inhibitor (TKI). A total of 657 patients were randomised in the study, of which 263 received carboplatin and pemetrexed (CP); and 131 which received RYBREVANT® in combination with carboplatin and pemetrexed (RYBREVANT®-CP). Additionally, 263 patients were randomised to receive RYBREVANT® in combination with lazertinib, carboplatin, and pemetrexed in a separate arm of the study. RYBREVANT® was administered intravenously at 1400 mg (for patients < 80 kg) or 1750 mg (for patients ≥ 80 kg) once weekly through 4 weeks, then every 3 weeks with a dose of 1750 mg (for patients < 80 kg) or 2100 mg (for patients ≥ 80 kg) starting at Week 7 until disease progression or unacceptable toxicity. Carboplatin was administered intravenously at area under the concentration-time curve 5 mg/mL per minute (AUC 5) once every 3 weeks, for up to 12 weeks. Pemetrexed was administered intravenously at 500 mg/m^2 once every 3 weeks until disease progression or unacceptable toxicity.

Patients were stratified by osimertinib line of therapy (first-line or second-line), prior brain metastases (yes or no), and Asian race (yes or no).

Of the 394 patients randomised to the RYBREVANT®-CP arm or CP arm, the median age was 62 (range: 31-85) years, with 38% of the patients ≥ 65 years of age; 60% were female; and 48% were Asian and 46% were White. Baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 (40%) or 1 (60%); 66% never smoked; 45% had history of brain metastasis, and 92% had Stage IV cancer at initial diagnosis.

RYBREVANT® in combination with carboplatin and pemetrexed demonstrated a statistically significant improvement in progression-free survival (PFS) compared to carboplatin and pemetrexed, with a HR of 0.48 (95% CI: 0.36, 0.64; p<0.0001). At the time of the second interim analysis for OS, with a median follow-up of approximately 18.6 months for RYBREVANT®-CP and approximately 17.8 months for CP, the OS HR was 0.73 (95%CI: 0.54, 0.99; p=0.0386). This was not statistically significant (tested at a prespecified significance level of 0.0142).

Efficacy results are summarised in Table 6.

Table 6: Efficacy results in MARIPOSA-2

	RYBREVANT®+ carboplatin+ pemetrexed (N=131)	**carboplatin+ pemetrexed (N=263)**
Progression-free survival (PFS)[a]		
Number of events (%)	74 (57)	171 (65)
Median, months (95% CI)	6.3 (5.6, 8.4)	4.2 (4.0, 4.4)
HR (95% CI); p-value	0.48 (0.36, 0.64); p<0.0001	
Overall survival (OS)		
Number of events (%)	65 (50)	143 (54)
Median, months (95% CI)	17.7 (16.0, 22.4)	15.3 (13.7, 16.8)

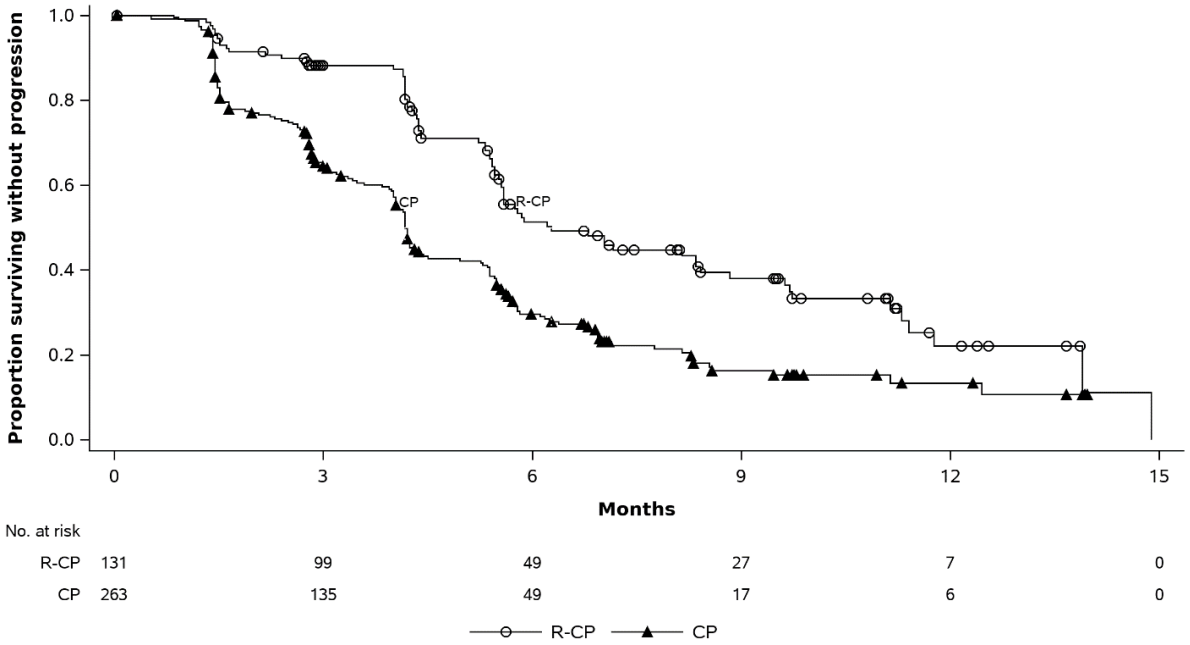
HR (95% CI); p-value[b]	0.73 (0.54, 0.99); p=0.0386	
Objective response rate[a]		
ORR, % (95% CI)	64% (55%, 72%)	36% (30%, 42%)
Odds Ratio (95% CI); p-value	3.10 (2.00, 4.80); p<0.0001	
Duration of response (DOR) [a]		
Median (95% CI), months	6.90 (5.52, NE)	5.55 (4.17, 9.56)
Patients with DOR ≥ 6 months	31.9%	20.0%

CI = Confidence Interval
NE = not estimable
PFS, DOR and ORR results are from data cut-off 10 July-2023 when hypothesis testing and final analysis for these endpoints was performed. OS results are from data cut-off 26 April 2024 from the second interim OS analysis.

[a] BICR-assessed

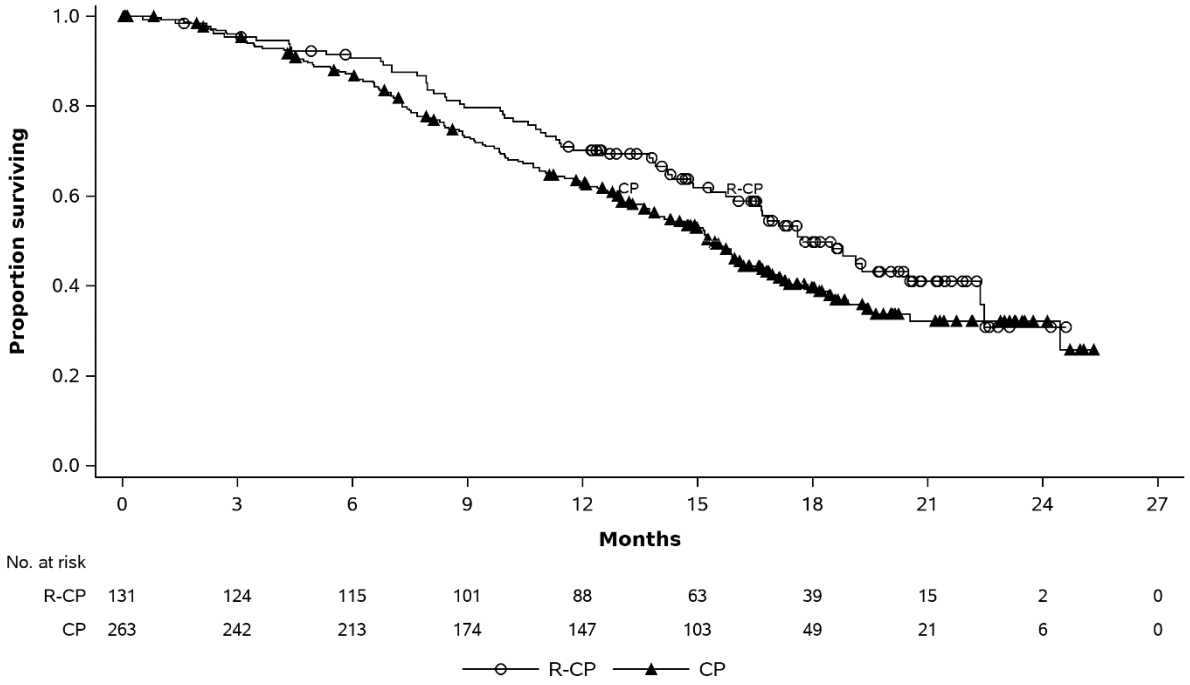
[b] The p-value is compared to a 2-sided significance level of 0.0142. Thus the OS results are not significant as of the second interim analysis.

Figure 1: Kaplan-Meier curve of PFS in previously treated NSCLC patients by BICR assessment



The PFS benefit of RYBREVANT®-CP compared to CP was consistent across all the predefined subgroups analysed, including ethnicity, age, gender, smoking history, and CNS metastases status at study entry.

Figure 2: Kaplan-Meier curve of OS in previously treated NSCLC patients



Intracranial metastases efficacy data
Patients with asymptomatic or previously treated and stable intracranial metastases were eligible to be randomised in MARIPOSA-2. Treatment with RYBREVANT®-CP was associated with a numeric increase in intracranial ORR (23.3% for RYBREVANT®-CP versus 16.7% for CP, odds ratio of 1.52; 95% CI (0.51, 4.50), and intracranial DOR (13.3 months; 95% CI (1.4, NE) in the RYBREVANT®-CP arm compared with 2.2 months; 95% CI (1.4, NE) in the CP arm). The median follow-up for RYBREVANT®-CP was approximately 18.6 months.

Previously-untreated non-small cell lung cancer (NSCLC) with Exon 20 insertion mutations (PAPILLON)
PAPILLON is a randomised, open-label, multicentre Phase 3 study comparing treatment with RYBREVANT® in combination with carboplatin and pemetrexed to chemotherapy alone (carboplatin and pemetrexed) in patients with treatment-naïve, locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations. Tumour tissue (92.2%) and/or plasma (7.8%) samples for all 308 patients were tested locally to determine EGFR Exon 20 insertion mutation status using next generation sequencing (NGS) in 55.5% of patients and/or polymerase chain reaction (PCR) in 44.5% of patients. Central testing was also performed using the AmoyDx® LC10 tissue test, Thermo Fisher Oncomine Dx Target Test, and the Guardant 360® CDx plasma test.

Patients with brain metastases at screening were eligible for participation once they were definitively treated, clinically stable, asymptomatic, and off corticosteroid treatment for at least 2 weeks prior to randomisation.

RYBREVANT® was administered intravenously at 1400 mg (for patients < 80 kg) or 1750 mg (for patients ≥ 80 kg) once weekly through 4 weeks, then every 3 weeks with a dose of 1750 mg (for patients < 80 kg) or 2100 mg (for patients ≥ 80 kg) starting at Week 7 until disease progression or unacceptable toxicity. Carboplatin was administered intravenously at area under the concentration-time curve 5 mg/mL per minute (AUC 5) once every 3 weeks, for up to 12 weeks. Pemetrexed was administered intravenously at 500 mg/m^2 once every 3 weeks until disease progression or unacceptable toxicity. Randomisation was stratified by ECOG performance status (0 or 1), and prior brain metastases (yes or no). Patients randomised to the carboplatin and pemetrexed arm who had confirmed disease progression were permitted to cross over to receive RYBREVANT® monotherapy.
A total of 308 subjects were randomised (1:1) to RYBREVANT® in combination with carboplatin and pemetrexed (N=153) or carboplatin and pemetrexed (N=155). The median age was 62 (range: 27 to 92) years, with 39% of the subjects ≥ 65 years of age; 58% were female; and 61% were Asian and 36% were White. Baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 (35%) or 1 (64%); 58% never smoked; 23% had history of brain metastasis and 84% had Stage IV cancer at initial diagnosis.

The primary endpoint for PAPILLON was PFS, as assessed by BICR. The median follow-up was14.9 months (range: 0.3 to 27.0).

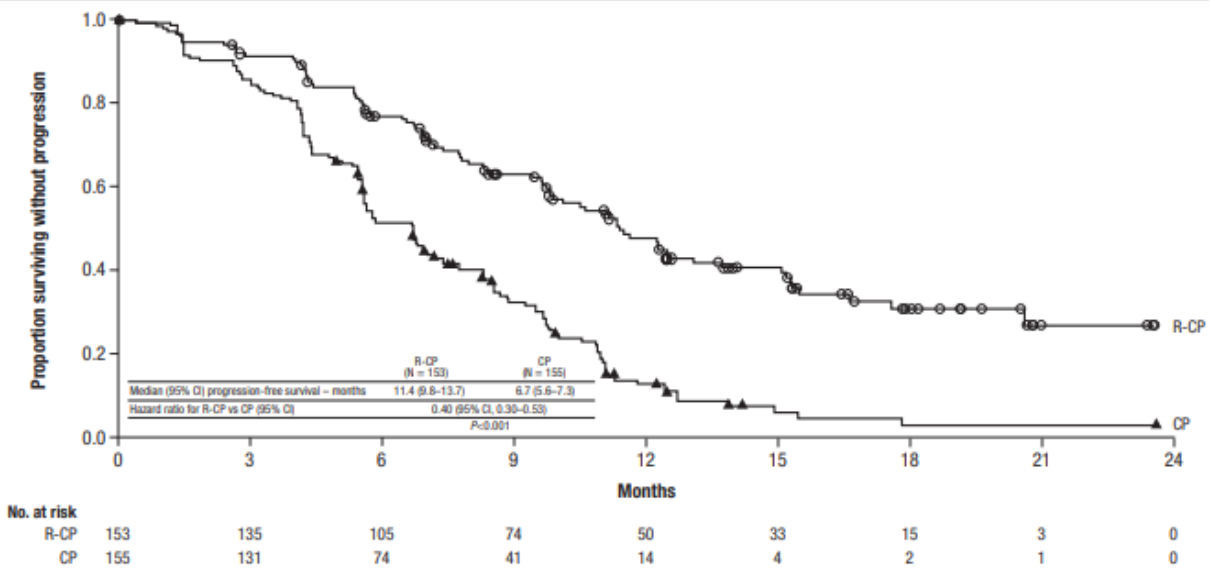
Efficacy results are summarised in Table 7.

Table 7: Efficacy results in PAPILLON

	RYBREVANT® + carboplatin+ pemetrexed (N=153)	carboplatin+ pemetrexed (N=155)
Progression-free survival (PFS) [a]		
Number of events	84 (55%)	132 (85%)
Median, months (95% CI)	11.4 (9.8, 13.7)	6.7 (5.6, 7.3)
HR (95% CI); p-value	0.395 (0.29, 0.52); p<0.0001	
Objective response rate[a, b]		
ORR, % (95% CI)	73% (65%, 80%)	47% (39%, 56%)
Odds ratio (95% CI); p-value	3.0 (1.8, 4.8); p<0.0001	
Complete response	3.9%	0.7%
Partial response	69%	47%
Overall survival (OS)[c]		
Number of events	40	52
Median OS, months (95% CI)	NE (28.3, NE)	28.6 (24.4, NE)
HR (95% CI); p-value	0.756 (0.50, 1.14); p=0.1825	

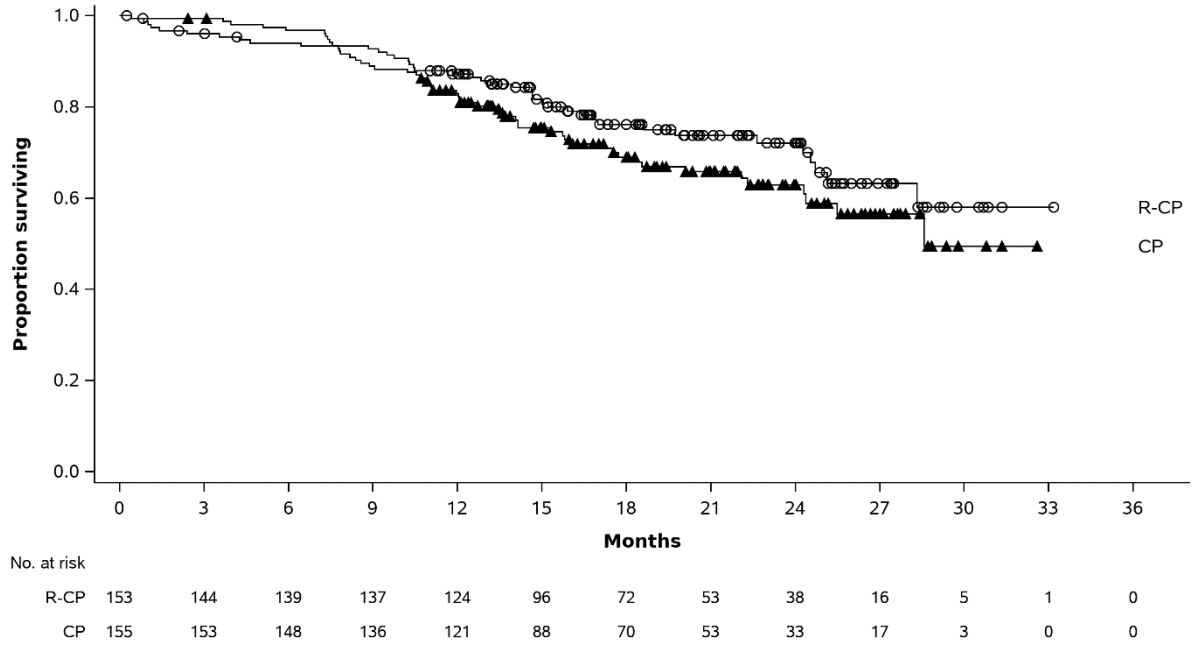
CI = confidence interval
NE = not estimable
[a] Blinded Independent Central Review by RECIST v1.1
[b] Based on Kaplan-Meier estimate.
[c] Based on the results of an updated OS with median follow-up of 20.9 months. The OS analysis was not adjusted for the potentially confounding effects of crossover (78 [50.3%] patients on the carboplatin + pemetrexed arm who received subsequent RYBREVANT® monotherapy treatment).

Figure 3: Kaplan-Meier curve of PFS in previously untreated NSCLC patients by BICR assessment



The PFS benefit of RYBREVANT® in combination with carboplatin and pemetrexed compared to carboplatin and pemetrexed was consistent across all the predefined subgroups of brain metastases at study entry (yes or no), age (< 65 or ≥ 65), sex (male or female), race (Asian or non-Asian), weight (< 80 kg or ≥ 80 kg), ECOG performance status (0 or 1), and smoking history (yes or no).

Figure 4: Kaplan-Meier curve of OS in previously untreated NSCLC patients by BICR assessment



Elderly

No overall differences in effectiveness were observed between patients ≥ 65 years of age and patients < 65 years of age.

5.2 Pharmacokinetic properties

Based on RYBREVANT® monotherapy data, amivantamab area under the concentration-time curve ($AUC_{1\ week}$) increases proportionally over a dose range from 350 to 1750 mg.

Based on simulations from the population pharmacokinetic model, $AUC_{1\ week}$ was approximately 2.8-fold higher after the fifth dose for the 2-week dosing regimen and 2.6-fold higher after the fourth dose for the 3-week dosing regimen. Steady-state concentrations of amivantamab were reached by Week 13 for both the 3-week and 2-week dosing regimen and the systemic accumulation was 1.9-fold.

Distribution

Based on the individual amivantamab PK parameter estimates in population PK analysis, the geometric mean (CV%) total volume of distribution, is 5.12 (27.8%) L, following administration of the recommended dose of RYBREVANT®.

Elimination

Based on the individual amivantamab PK parameter estimates in population PK analysis, the geometric mean (CV%) linear clearance (CL) and terminal half-life associated with linear clearance is 0.266 (30.4%) L/day and 13.7 (31.9%) days respectively.

Special populations

Elderly
No clinically meaningful differences in the pharmacokinetics of amivantamab were observed based on age (27-87 years).

Renal impairment
No clinically meaningful effect on the pharmacokinetics of amivantamab was observed in patients with mild (60 ≤ creatinine clearance [CrCl] < 90 mL/min) and moderate (29 ≤ CrCl < 60 mL/min) renal impairment. The effect of severe renal impairment (15 ≤ 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 metabolised through hepatic pathways.

No clinically meaningful effect in the pharmacokinetics of amivantamab was observed based on mild hepatic impairment [(total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5 x 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.

Paediatric population
The pharmacokinetics of RYBREVANT® in paediatric patients have not been investigated.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity.

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 animal studies have been conducted to evaluate the effects on reproduction and foetal development; however, based on its mechanism of action, amivantamab can cause foetal harm or developmental anomalies. As reported in the literature, reduction, elimination, or disruption of embryo foetal or maternal EGFR signalling can prevent implantation, cause embryo foetal loss during various stages of gestation (through effects on placental development), cause developmental anomalies in multiple organs or early death in surviving foetuses. Similarly, knock out of MET or its ligand hepatocyte growth factor (HGF) was embryonic lethal due to severe defects in placental development, and foetuses 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 foetus.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethylenediaminetetraacetic acid (EDTA) disodium salt dihydrate
L-Histidine
L-Histidine hydrochloride monohydrate
L-Methionine
Polysorbate 80 (E433)
Sucrose
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
3 years

After dilution
Chemical and physical in-use stability has been demonstrated for 10 hours at 15°C to 25°C in room light. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (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 section 6.3.

6.5 Nature and contents of container

7 mL concentrate in a Type 1 glass vial with an elastomeric closure and aluminium seal with a flip-off cap containing 350 mg amivantamab. Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

Prepare the solution for intravenous infusion using aseptic technique as follows:

Preparation
- Determine the dose required and the number of RYBREVANT® vials needed based on patient's baseline weight (see section 4.2). Each vial contains 350 mg of amivantamab.
- For every 3-week dosing, patients < 80 kg receive 1400 mg once weekly for a total of 4 doses, then 1750 mg every 3 weeks starting at Week 7, and for patients ≥ 80 kg, 1750 mg once weekly for a total of 4 doses, then 2100 mg every 3 weeks starting at Week 7.
- Check that the RYBREVANT® solution is colourless to pale yellow. Do not use if discolouration or visible particles are present.
- Withdraw and then discard a volume of either 5% glucose solution or sodium chloride 9 mg/mL (0.9%) solution for injection from the 250 mL infusion bag that is equal to the required volume of RYBREVANT® solution to be added (discard 7 mL diluent from the infusion bag for each vial). Infusion bags must be made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE), or polyolefin blend (PP+PE).
- Withdraw 7 mL of RYBREVANT® from each vial needed then add it to the infusion bag. Each vial contains a 0.5 mL overfill to ensure sufficient extractable volume. 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.
- Visually inspect for particulate matter and discolouration prior to administration. Do not use if discolouration or visible particles are observed.

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 0.22 or 0.2 micrometre). Administration sets must be made of either polyurethane (PU), polybutadiene (PBD), PVC, PP, or PE.
- The administration set with filter must be primed with either 5% glucose solution or 0.9% sodium chloride solution prior to the initiation of each RYBREVANT® infusion.
- Do not infuse RYBREVANT® concomitantly in the same intravenous line with other agents.
- The diluted solution should be administered within 10 hours (including infusion time) at room temperature (15°C to 25°C) and in room light.

- Due to the frequency of IRRs at the first dose, amivantamab should be infused via a peripheral vein at Week 1 and Week 2; infusion via a central line may be administered for subsequent weeks when the risk of IRR is lower. See infusion rates in section 4.2.

Disposal
This medicinal product is for single use only and any unused medicinal product that is not administered within 10 hours should be disposed of in accordance with local requirements.

HOW SUPPLIED
RYBREVANT® concentrate for solution for infusion
Box, 1 vial @ 350 mg/7 mL
Reg. No.: DKI2560002149A1

Date of first Authorisation: 28 October 2025

Prescription Drug

HARUS DENGAN RESEP DOKTER

Manufactured by Cilag AG, Schaffhausen, Switzerland
Registered by PT Integrated Healthcare Indonesia, Jakarta – Indonesia
For adverse event and product quality complaint please contact drugsafety@jacid.jnj.com

Based on EU SmPC 20250821

INFORMASI PRODUK UNTUK PASIEN

RYBREVANT® 350 mg larutan konsentrat untuk infus
Amivantamab

Baca informasi ini secara seksama sebelum Anda mulai menggunakan obat ini karena mengandung informasi penting untuk Anda:
- Simpan informasi produk ini. Anda mungkin perlu untuk membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau perawat Anda.
- Jika Anda mendapatkan efek samping, laporkan kepada dokter atau perawat Anda. Termasuk efek samping yang mungkin tidak tercantum dalam informasi produk ini. Lihat bagian 4.

Apa yang ada dalam informasi produk ini

1. Apa itu RYBREVANT® dan digunakan untuk apa

Apa itu RYBREVANT®
RYBREVANT® adalah obat kanker. Mengandung zat aktif 'amivantamab', yaitu antibodi (sejenis protein) yang dirancang untuk mengenali dan menempel pada target tertentu di dalam tubuh.

Apa Kegunaan RYBREVANT®
RYBREVANT® digunakan pada orang dewasa dengan jenis kanker yang disebut 'Kanker Paru Jenis Karsinoma Bukan Sel Kecil (KPKBSK)'. Obat ini digunakan ketika kanker telah menyebar ke bagian lain tubuh Anda dan telah mengalami perubahan tertentu dalam gen yang disebut ‘EGFR’.
RYBREVANT® dapat diresepkan untuk Anda:
- dikombinasikan dengan kemoterapi (carboplatin dan pemetrexed) setelah terjadi kegagalan terapi dengan obat Osimertinib monoterapi.
- sebagai obat pilihan pertama yang Anda terima untuk kanker Anda yang dikombinasikan dengan kemoterapi (carboplatin dan pemetrexed).

Bagaimana RYBREVANT® bekerja
Zat aktif dalam RYBREVANT® , yaitu amivantamab, menargetkan dua protein yang ditemukan pada sel kanker:
- *epidermal growth factor receptor (EGFR),* dan
- *mesenchymal epithelial transition factor (MET).*

Obat ini bekerja dengan cara menempel pada protein tersebut. Obat ini dapat membantu memperlambat atau menghentikan pertumbuhan kanker paru-paru Anda. Obat ini juga dapat membantu mengurangi ukuran tumor.

RYBREVANT® dapat diberikan dalam kombinasi dengan obat anti kanker lainnya. Penting bagi Anda juga untuk membaca brosur kemasan obat-obatan lainnya. Jika Anda memiliki pertanyaan tentang obat-obatan lainnya, tanyakan kepada dokter Anda.

2. Apa saja yang perlu Anda ketahui sebelum menggunakan RYBREVANT®

Anda tidak boleh diberikan RYBREVANT® :
- Jika Anda alergi terhadap amivantamab atau bahan lain dari obat ini (tercantum pada bagian 6).

Jangan menggunakan RYBREVANT® jika kondisi di atas berlaku pada Anda. Jika Anda tidak yakin, bicarakan dengan dokter atau perawat Anda sebelum Anda diberikan RYBREVANT®.

Peringatan dan Perhatian
Bicaralah dengan dokter atau perawat Anda sebelum menggunakan RYBREVANT®, jika:
- Anda menderita radang paru-paru (suatu kondisi yang disebut 'penyakit paru interstitial' atau 'pneumonitis').

Beritahu dokter atau perawat Anda segera mungkin jika saat meminum obat ini Anda mengalami salah satu efek samping berikut (lihat bagian 4 untuk informasi lebih lanjut):
- Efek samping apa pun pada saat obat ini diberikan ke pembuluh darah Anda/ pada saat diinfus.
- Tiba-tiba kesulitan bernapas, batuk, atau demam yang mungkin menandakan peradangan paru-paru.
- Masalah kulit. Untuk mengurangi risiko timbulnya masalah kulit, jauhi sinar matahari, kenakan pakaian pelindung, oleskan tabir surya, dan gunakan pelembab secara rutin pada kulit dan kuku saat mengonsumsi obat ini. Anda harus terus melakukan ini selama 2 bulan setelah Anda menghentikan pengobatan.
- Masalah mata. Jika Anda memiliki masalah penglihatan atau sakit mata, segera hubungi dokter atau perawat Anda. Jika Anda menggunakan lensa kontak dan mengalami gejala mata baru, hentikan penggunaan lensa kontak dan segera beri tahu dokter.

Anak-anak dan remaja
Jangan berikan RYBREVANT® pada anak-anak atau remaja di bawah usia 18 tahun. Hal ini dikarenakan belum diketahui bagaimana obat ini akan mempengaruhi mereka.

Penggunaan obat-obatan lain dan RYBREVANT®
Beritahu dokter atau perawat Anda jika Anda sedang mengonsumsi, baru saja mengonsumsi atau mungkin mengonsumsi obat-obatan lain.

Kontrasepsi
- Wanita yang sedang diberikan RYBREVANT® harus menggunakan kontrasepsi yang efektif selama pengobatan dan selama 3 bulan setelah pengobatan.

Kehamilan
- Jika Anda hamil, berpikir Anda mungkin sedang hamil atau berencana untuk memiliki bayi, mintalah petunjuk dokter Anda sebelum Anda diberikan obat ini.
- Ada kemungkinan bahwa obat ini dapat membahayakan bayi yang belum lahir. Jika Anda hamil saat menjalani pengobatan ini, segera beritahu dokter atau perawat Anda. Anda dan dokter Anda akan memutuskan apakah manfaat pengobatan ini lebih besar daripada risikonya pada bayi Anda.

Menyusui
Belum diketahui apakah RYBREVANT® masuk ke dalam ASI. Mintalah saran dokter sebelum mengonsumsi obat ini. Anda dan dokter Anda akan memutuskan apakah manfaat menyusui lebih besar dibandingkan risikonya terhadap bayi Anda.

Mengemudi dan menggunakan mesin
Jika Anda merasa lelah, pusing, atau jika mata Anda iritasi atau penglihatan terpengaruh setelah mengonsumsi RYBREVANT® , jangan mengemudi atau menggunakan peralatan mesin.

RYBREVANT® mengandung natrium
Obat ini mengandung kurang dari 1 mmol natrium (23 mg) dalam 7 mL, artinya bisa dikatakan "bebas sodium". Namun, sebelum RYBREVANT® diberikan kepada Anda, ada kemungkinan obat ini dapat dicampur dengan larutan yang mengandung natrium. Bicaralah dengan dokter Anda jika Anda sedang menjalani diet rendah garam.

RYBREVANT® mengandung polisorbat
Obat ini mengandung 0,6 mg polisorbat 80 dalam tiap mL, setara dengan 4,2 mg per vial 7 mL. Polisorbat dapat menyebabkan reaksi alergi. Beritahu dokter Anda jika Anda memiliki alergi yang diketahui terhadap Polisorbat.

3. Bagaimana RYBREVANT® diberikan

Berapa banyak obat ini diberikan
Dokter Anda akan menentukan dosis RYBREVANT® yang tepat untuk Anda. Dosis obat ini akan tergantung pada berat badan Anda pada awal terapi. Anda akan dirawat dengan RYBREVANT® setiap 3 minggu sekali sesuai dengan pengobatan yang ditentukan dokter untuk Anda.

Dosis RYBREVANT® yang dianjurkan setiap 3 minggu adalah:
- 1400 mg untuk 4 dosis pertama dan 1750 mg untuk dosis berikutnya jika berat badan Anda kurang dari 80 kg.
- 1750 mg untuk 4 dosis pertama dan 2100 mg untuk dosis berikutnya jika berat badan Anda lebih dari atau sama dengan 80 kg.

Bagaimana obat ini diberikan
Obat ini akan diberikan kepada Anda oleh dokter atau perawat. Obat ini diberikan melalui infus ke pembuluh darah ('infus intravena') selama beberapa jam.

RYBREVANT® diberikan sebagai berikut:
- seminggu sekali selama 4 minggu pertama
- kemudian setiap 3 minggu sekali mulai minggu ke 7, selama Anda tetap mendapatkan manfaat dari pengobatan tersebut.

Pada minggu pertama, dokter Anda akan memberi Anda dosis RYBREVANT® yang dibagi menjadi dua hari.

Obat-obatan yang diberikan selama pengobatan dengan RYBREVANT®
Sebelum penggunaan obat infus RYBREVANT®, Anda akan diberikan obat-obatan yang membantu menurunkan kemungkinan reaksi akibat infus, yaitu:
- obat-obatan untuk anti alergi (antihistamin)
- obat anti radang (kortikosteroid)
- obat demam (misalnya parasetamol).

Anda mungkin juga diberikan obat tambahan berdasarkan gejala apa pun yang mungkin Anda alami.

Jika Anda diberi RYBREVANT® lebih dari yang seharusnya
Obat ini akan diberikan oleh dokter atau perawat Anda. Jika pada kejadian yang sangat jarang terjadi Anda diberi dosis terlalu banyak (overdosis), dokter Anda akan memeriksa Anda untuk melihat efek samping yang mungkin terjadi.

Jika Anda melupakan jadwal Anda untuk mendapatkan RYBREVANT®
Hal yang sangat penting untuk mengikuti jadwal penggunaan obat ini. Jika Anda melewatkan satu jadwal, buatlah janji lain sesegera mungkin.

Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter atau perawat Anda.

4. Efek samping

Seperti semua obat lainnya, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.

Efek samping serius
Beritahu dokter atau perawat Anda segera jika Anda merasakan tanda-tanda efek samping sebagai berikut:

Sangat umum (dapat dialami lebih dari 1 dari 10 orang):
- Tanda-tanda reaksi akibat infus - seperti menggigil, sesak napas, rasa mual, muka memerah, dada tidak nyaman dan muntah-muntah saat obat diberikan. Hal ini bisa terjadi terutama pada dosis pertama. Dokter Anda mungkin memberi Anda obat lain, atau infus mungkin perlu diperlambat atau dihentikan.
- Masalah kulit – seperti ruam (termasuk jerawat), kulit sekitar kuku yang terinfeksi, kulit kering, gatal, nyeri, dan kemerahan. Beritahu dokter Anda jika masalah kulit atau kuku Anda semakin parah.

Umum (mempengaruhi hingga 1 dari 10 orang) yaitu:
- Masalah mata – seperti mata kering, kelopak mata bengkak, mata gatal, gangguan penglihatan, tumbuhnya bulu mata.
- Tanda-tanda peradangan pada paru-paru - seperti kesulitan bernapas secara tiba-tiba, batuk, atau demam. Hal ini dapat menyebabkan kerusakan permanen ('penyakit paru interstisial'). Dokter Anda mungkin ingin menghentikan Rybrevant jika Anda mengalami efek samping ini.

Jarang (mempengaruhi hingga 1 dari 100 orang):
- Peradangan pada kornea (bagian depan mata)
- peradangan di dalam mata yang dapat mempengaruhi penglihatan
- Ruam yang mengancam nyawa disertai lepuh dan kulit terkelupas di sebagian besar tubuh (nekrolisis epidermal toksik).

Efek samping berikut telah dilaporkan dalam studi klinis pada penggunaan RYBREVANT® yang dikombinasikan dengan kemoterapi (carboplatin dan pemetrexed):

Sangat umum (dapat dialami lebih dari 1 dari 10 orang):
- rendahnya jumlah suatu jenis sel darah putih (neutropenia)
- rendahnya jumlah 'trombosit' (sel yang membantu pembekuan darah)
- bekuan darah di pembuluh darah vena
- merasa sangat lelah
- mual
- luka di mulut
- sembelit
- pembengkakan akibat penumpukan cairan di dalam tubuh
- nafsu makan berkurang
- rendahnya kadar protein 'albumin' dalam darah
- peningkatan kadar enzim hati 'alanin aminotransferase' dalam darah, kemungkinan merupakan tanda adanya masalah hati
- peningkatan kadar enzim 'aspartate aminotransferase' dalam darah, kemungkinan merupakan tanda adanya masalah hati
- muntah
- rendahnya kadar kalium dalam darah
- diare
- demam
- rendahnya kadar magnesium dalam darah
- rendahnya kadar kalsium dalam darah.

Umum (dapat dialami hingga 1 dari 10 orang):
- peningkatan kadar enzim 'alkaline fosfatase' dalam darah
- sakit perut
- merasa pusing
- wasir
- nyeri otot
- Luka (borok) di kulit.

5. Bagaimana cara menyimpan RYBREVANT®

RYBREVANT® disimpan di rumah sakit atau klinik.

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah masa kedaluwarsa yang tertera pada dus dan label setelah tulisan EXP. Tanggal kedaluwarsa mengacu pada hari terakhir pada bulan tersebut.

Stabilitas obat setelah terkena zat kimia dan secara fisik masih bisa digunakan selama 10 jam pada suhu 15°C hingga 25°C dalam ruangan terang. Dari sudut pandang mikrobiologi, kecuali metode pengenceran menghilangkan risiko kontaminasi mikroba, produk harus segera digunakan. Jika tidak segera digunakan, waktu dan kondisi penyimpanan yang digunakan adalah tanggung jawab pengguna.

Simpan dalam suhu 2°C - 8°C. Jangan dibekukan.

Simpan pada kemasan asli untuk melindungi dari cahaya.

Jangan membuang obat apa pun melalui air limbah atau limbah rumah tangga. Tenaga kesehatan Anda akan membuang obat-obatan yang tidak lagi digunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lainnya

Apa kandungan RYBREVANT®

- Bahan aktifnya adalah amivantamab. Satu mL konsentrat larutan infus mengandung 50 mg amivantamab. Satu botol konsentrat 7 mL mengandung 350 mg amivantamab.
- Bahan lainnya adalah asam etilendiamintetraasetat (EDTA) disodium salt dihydrate, L-histidin, L-histidin hidroklorida monohidrat, L-metionin, polisorbat 80, sukrosa, dan air untuk injeksi (lihat bagian 2).

Seperti apa RYBREVANT® terlihat dan isi kemasannya
RYBREVANT® adalah cairan konsentrat untuk infus dan merupakan cairan bening hingga kuning pucat. Obat ini tersedia dalam kemasan karton berisi 1 vial kaca berisi 7 mL konsentrat.

No. Reg: DKI2560002149A1

HARUS DENGAN RESEP DOKTER

Diproduksi oleh: Cilag AG, Schaffhausen, Switzerland.

Didaftarkan oleh: PT Integrated Healthcare Indonesia, Jakarta – Indonesia

Untuk pelaporan efek samping dan keluhan kualitas produk, dapat menghubungi drugsafety@jacid.jnj.com

Informasi berikut ditujukan untuk profesional kesehatan saja:

Produk obat ini tidak boleh dicampur dengan produk obat lain kecuali yang disebutkan di bawah ini.

Siapkan larutan infus intravena dengan teknik aseptik sebagai berikut:

Persiapan

- Tentukan dosis yang dibutuhkan dan jumlah vial RYBREVANT® yang dibutuhkan berdasarkan berat awal pasien. Setiap botol RYBREVANT® mengandung 350 mg amivantamab.

- Untuk dosis setiap 3 minggu, pasien < 80 kg menerima 1400 mg sekali seminggu dengan total 4 dosis, kemudian 1750 mg setiap 3 minggu dimulai pada Minggu ke 7, dan untuk pasien ≥ 80 kg menerima 1750 mg sekali seminggu dengan total 4 dosis kemudian 2100 mg setiap 3 minggu mulai Minggu ke 7.
- Periksa apakah larutan RYBREVANT® berwarna bening hingga kuning pucat. Jangan gunakan jika ada perubahan warna atau partikel yang terlihat.
- Ambil larutan glukosa 5% atau larutan natrium klorida 9 mg/mL (0,9%) untuk injeksi dari kantong infus 250 mL yang setara dengan volume larutan RYBREVANT® yang perlu ditambahkan (buang 7 mL pengencer dari kantong infus untuk setiap vial). Kantong infus harus terbuat dari polivinilklorida (PVC), polipropilen (PP), polietilen (PE), atau campuran poliolefin (PP+PE).
- Ambil 7 mL RYBREVANT® dari setiap vial yang diperlukan lalu masukkan ke dalam kantong infus. Setiap botol berisi 0,5 mL pengisian berlebih untuk memastikan volume ekstrak yang cukup. Volume akhir dalam kantong infus harus 250 mL. Buang sisa bagian yang tidak terpakai di dalam botol.
- Balikkan kantong secara perlahan untuk mencampur larutan. Jangan diaduk/digoyang.
- Periksa secara visual apakah ada partikel dan perubahan warna sebelum pemberian. Jangan gunakan jika terlihat perubahan warna atau partikel yang terlihat.

Pemberian

- Berikan larutan obat yang telah diencerkan melalui infus intravena menggunakan set infus yang dilengkapi dengan pengatur aliran dan dengan filter polietersulfon (PES) pengikat protein rendah, steril, non pirogenik, dan inline (ukuran pori 0,22 atau 0,2 mikrometer). Perangkat infus harus terbuat dari poliuretan (PU), polibutadiena (PBD), PVC, PP, atau PE.
- Perangkat infus dengan filter harus diisi dengan larutan glukosa 5% atau larutan natrium klorida 0,9% sebelum memulai setiap infus RYBREVANT®.
- Jangan memasukkan RYBREVANT® secara bersamaan dalam jalur intravena yang sama dengan obat lain.
- Larutan obat harus diberikan dalam waktu 10 jam (termasuk waktu infus) pada suhu kamar (15°C hingga 25°C) dan dalam ruangan terang.
- Karena reaksi infus pada dosis pertama, amivantamab harus diberikan melalui vena perifer pada Minggu 1 dan Minggu 2; infus melalui jalur sentral dapat diberikan pada minggu-minggu berikutnya ketika risiko reaksi infus lebih rendah.

Pembuangan

Produk obat ini hanya untuk sekali pakai dan produk obat apa pun yang tidak digunakan dan tidak diberikan dalam waktu 10 jam harus dibuang sesuai dengan persyaratan setempat.

Berdasarkan EU SmPC 20250821