

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## **1. NAME OF THE MEDICINAL PRODUCT**

Rybrevent 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.

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**

Rybrevent as monotherapy is indicated for treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations, after failure of platinum-based therapy.

### **4.2 Posology and method of administration**

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

Rybrevent 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 Rybrevent therapy, EGFR Exon 20 insertion mutation-positive status must be established using a validated test method (see section 5.1).

#### Posology

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

The recommended dose of Rybrevent is provided in Table 1, and the dosing schedule is provided in Table 2 (see below “Infusion rates”).

**Table 1: Recommended dose of Rybrevant**

Body weight of patient (at baseline*)	Recommended dose	Number of vials
Less than 80 kg	1,050 mg	3
Greater than or equal to 80 kg	1,400 mg	4

\* Dose adjustments not required for subsequent body weight changes

**Table 2: Dosing schedule for Rybrevant**

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

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  $\leq$  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 3. See also specific dose modifications for specific adverse reactions below Table 3.

**Table 3: Recommended dose modifications for adverse reactions**

Body weight (at baseline)	Initial dose	1 <sup>st</sup> dose modification	2 <sup>nd</sup> dose modification	3 <sup>rd</sup> dose modification
Less than 80 kg	1,050 mg	700 mg	350 mg	Discontinue Rybrevant
Greater than or equal to 80 kg	1,400 mg	1,050 mg	700 mg	

Infusion-related reactions

Interrupt infusion 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 Table 5). Concomitant medicinal products should be administered at the next dose (see Table 4).
- Recurrent Grade 3 or Grade 4 (life-threatening): Permanently discontinue Rybrevant.

Skin and nail reactions

If the patient develops a Grade 2 skin or nail reaction, supportive care should be initiated; if there is no improvement after 2 weeks, dose reduction should be considered (see Table 3). 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  $\leq$  Grade 2, Rybrevant should be resumed at a reduced dose. If the patient develops Grade 4 skin reactions (including toxic epidermal necrolysis (TEN)), permanently discontinue Rybrevant (see section 4.4).

Interstitial lung disease

If the patient develops interstitial lung disease (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 4). For subsequent doses, antihistamines and antipyretics are required to be administered. Antiemetics should be administered as needed.

**Table 4: 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 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.

### 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 5 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 5: Infusion rates for Rybrevant administration**

1,050 mg dose			
Week	Dose (per 250 mL bag)	Initial infusion rate	Subsequent infusion rate <sup>‡</sup>
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	1,050 mg	85 mL/hr	
Subsequent weeks*	1,050 mg	125 mL/hr	
1,400 mg dose			
Week	Dose (per 250 mL bag)	Initial infusion rate	Subsequent infusion rate <sup>‡</sup>
Week 1 (split dose infusion)			
Week 1 Day 1	350 mg	50 mL/hr	75 mL/hr
Week 1 Day 2	1,050 mg	35 mL/hr	50 mL/hr
Week 2	1,400 mg	65 mL/hr	
Week 3	1,400 mg	85 mL/hr	
Subsequent weeks*	1,400 mg	125 mL/hr	

\* After 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 IRRs.

### 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 should be evaluated and appropriate treatment should be initiated as necessary. Rybrevant should be permanently discontinued in patients with confirmed ILD (see section 4.2).

#### Skin and nail reactions

Rash (including dermatitis acneiform), pruritus and dry skin 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. 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).

### **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**

Rybrevent 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

The most frequent adverse reactions in all grades were rash (76%), infusion-related reactions (67%), nail toxicity (47%), hypoalbuminaemia (31%), oedema (26%), fatigue (26%), stomatitis (24%), nausea (23%), and constipation (23%). Serious adverse reactions included ILD (1.3%), IRR (1.1%), and rash (1.1%). Three percent of patients discontinued Rybrevent due to adverse reactions. The most frequent adverse reactions leading to treatment discontinuation were IRR (1.1%), ILD (0.5%), and nail toxicity (0.5%).

### Tabulated list of adverse reactions

Table 6 summarises the adverse drug reactions that occurred in patients receiving amivantamab.

The data reflects exposure to amivantamab in 380 patients with locally advanced or metastatic non-small cell lung cancer after failure of platinum-based chemotherapy. Patients received amivantamab 1,050 mg (for patients < 80 kg) or 1,400 mg (for patients ≥ 80 kg). The median exposure to amivantamab was 4.1 months (range: 0.0 to 39.7 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 (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (frequency cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

**Table 6: Adverse reactions in patients receiving amivantamab**

System organ class Adverse reaction	Frequency category	Any Grade (%)	Grade 3-4 (%)
Metabolism and nutrition disorders			
Hypoalbuminaemia <sup>a</sup> (see section 5.1)	Very common	31	2*
Decreased appetite		16	0.5*
Hypocalcaemia		10	0.3*
Nervous system disorders			
Dizziness <sup>b</sup>	Very common	13	0.3*

Eye disorders			
Visual impairment <sup>c</sup>	Common	3	0
Growth of eyelashes <sup>d</sup>		1	0
Other eye disorders <sup>e</sup>		6	0
Keratitis	Uncommon	0.5	0
Uveitis		0.3	0
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease <sup>f</sup>	Common	3	0.5*
Gastrointestinal disorders			
Diarrhoea	Very common	11	2*
Stomatitis <sup>g</sup>		24	0.5*
Nausea		23	0.5*
Constipation		23	0
Vomiting		12	0.5*
Abdominal pain <sup>h</sup>	Common	9	0.8*
Hepatobiliary disorders			
Alanine aminotransferase increased	Very common	15	2
Aspartate aminotransferase increased		13	1
Blood alkaline phosphatase increased		12	0.5*
Skin and subcutaneous tissue disorders			
Rash <sup>i</sup>	Very common	76	3*
Nail toxicity <sup>j</sup>		47	2*
Dry skin <sup>k</sup>		19	0
Pruritus		18	0
Toxic epidermal necrolysis	Uncommon	0.3	0.3*
Musculoskeletal and connective tissue disorders			
Myalgia	Very common	11	0.3*
General disorders and administration site conditions			
Oedema <sup>l</sup>	Very common	26	0.8*
Fatigue <sup>m</sup>		26	0.8*
Injury, poisoning and procedural complications			
Infusion-related reaction	Very common	67	2

\* Grade 3 events only

<sup>a</sup> Hypoalbuminaemia: blood albumin decreased, hypoalbuminaemia

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

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

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

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

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

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

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

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

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

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

<sup>l</sup> Oedema: eye oedema, eyelid oedema, face oedema, generalised oedema, localised oedema, oedema, oedema peripheral, periorbital oedema, periorbital swelling, peripheral swelling, swelling face

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



## Description of selected adverse reactions

### Infusion-related reactions

Infusion-related reactions occurred in 67% of patients treated with amivantamab. Ninety-eight percent of IRRs were Grade 1-2. Ninety-nine percent of IRRs occurred at the first infusion with a median time to onset of 60 minutes, and the majority occurring within 2 hours of infusion start. The most frequent signs and symptoms include chills, dyspnoea, nausea, flushing, chest discomfort, and vomiting (see section 4.4).

### 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 2.6% of patients. 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), pruritus, and dry skin occurred in 76% of patients treated with amivantamab. Most cases were Grade 1 or 2, with Grade 3 rash events occurring in 3% of patients. Rash leading to amivantamab discontinuation occurred in 0.3% of patients. Rash usually developed within the first 4 weeks of therapy, with a median time to onset of 14 days. Paronychia occurred in patients treated with amivantamab. Most events were Grade 1 or 2, with Grade 3 paronychia occurring in 1.8% of patients (see section 4.4).

### Eye disorders

Eye disorders, including keratitis (0.5%), occurred in 9% of patients treated with amivantamab. Other reported adverse reactions included growth of eyelashes, visual impairment, and other eye disorders. All events were Grade 1-2 (see section 4.4).

## Other 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  $\geq 65$  years of age and patients  $< 65$  years of age.

### Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. In a clinical study of patients with locally advanced or metastatic NSCLC treated with amivantamab, 3 (0.9%) of the 347 evaluable patients tested positive for 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 via the national reporting system listed in Appendix V.

## **4.9 Overdose**

No maximum tolerated dose has been determined in a clinical study in which patients received up to 1,750 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 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

CHRYSLIS is a multicentre, open-label, multi-cohort study conducted to assess the safety and efficacy of Rybrevant in patients with locally advanced or metastatic NSCLC. Efficacy was evaluated in 114 patients with locally advanced or metastatic NSCLC who had EGFR Exon 20 insertion mutations, whose disease had progressed on or after platinum-based chemotherapy, and who had a median follow-up of 12.5 months. Tumour tissue (93%) and/or plasma (10%) samples for all patients were tested locally to determine EGFR Exon 20 insertion mutation status using next generation sequencing (NGS) in 46% of patients and/or polymerase chain reaction (PCR) in 41% of patients; for 4% of patients, the testing methods were not specified. Patients with untreated brain metastases or a history of ILD requiring treatment with prolonged steroids or other immunosuppressive agents within the last 2 years were not eligible for the study. Rybrevant was administered intravenously at 1,050 mg for patients < 80 kg or 1,400 mg for patients ≥ 80 kg once weekly for 4 weeks, then every 2 weeks starting at Week 5 until loss of clinical benefit or unacceptable toxicity. The primary efficacy endpoint was investigator-assessed overall response rate (ORR), defined as confirmed complete response (CR) or partial response (PR) based on RECIST v1.1. In addition, the primary endpoint was assessed by a blinded independent central review (BICR). Secondary efficacy endpoints included duration of response (DOR).

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

Efficacy results are summarised in Table 7.

**Table 7: Efficacy results in CHRYSALIS**

	<b>Investigator assessment (N=114)</b>
<b>Overall response rate<sup>a, b</sup> (95% CI)</b>	37% (28%, 46%)
Complete response	0%
Partial response	37%
<b>Duration of response</b>	
Median <sup>c</sup> (95% CI), months	12.5 (6.5, 16.1)
Patients with DOR $\geq$ 6 months	64%

CI = Confidence Interval

<sup>a</sup> Confirmed response

<sup>b</sup> ORR and DOR results by investigator assessment were consistent with those reported by BICR assessment; ORR by BICR assessment was 43% (34%, 53%), with a 3% CR rate and a 40% PR rate, median DOR by BICR assessment was 10.8 months (95% CI: 6.9, 15.0), and patients with DOR  $\geq$  6 months by BICR assessment was 55%.

<sup>c</sup> Based on Kaplan-Meier estimate.

Anti-tumour activity was observed across studied mutation subtypes.

#### Elderly

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

#### Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Rybrevant in all subsets of the paediatric population in non-small cell lung cancer (see section 4.2 for information on paediatric use).

#### Conditional approval

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

## **5.2 Pharmacokinetic properties**

Amivantamab area under the concentration-time curve ( $AUC_{1 \text{ week}}$ ) increases proportionally over a dose range from 350 to 1,750 mg.

Following administration of Rybrevant at the recommended dose and schedule, the mean serum  $AUC_{1 \text{ week}}$  was approximately 2.9-fold higher after the fifth dose, following the weekly dosing, compared to the first dose.

Steady state was achieved approximately 2 months into the every 2-week dosing period (by the ninth infusion) at 1,050 mg, and the mean serum  $AUC_{1 \text{ week}}$  was approximately 2.4 fold higher at steady state compared to the first dose.

#### Distribution

Amivantamab geometric mean (CV%) total volume of distribution, based on population PK parameter estimates, was 5.37 (21%) L following administration of the recommended dose of Rybrevant.

#### Elimination

Amivantamab clearance is higher with low doses (< 350 mg) but linear within the clinical dose range. The geometric mean (CV%) linear clearance was estimated to be 225 (25%) mL/day, based on population PK modelling. The geometric mean (CV%) terminal half-life associated with linear

clearance, derived based on population PK parameter estimates, was 15.7 (26%) days, following administration of the recommended dose of Rybrevant as monotherapy.

### Special populations

#### Elderly

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

#### Renal impairment

No clinically meaningful effect on the pharmacokinetics of amivantamab was observed in patients with mild ( $60 \leq \text{creatinine clearance [CrCl]} < 90 \text{ mL/min}$ ) and moderate ( $29 \leq \text{CrCl} < 60 \text{ mL/min}$ ) renal impairment. The effect of severe renal impairment ( $15 \leq \text{CrCl} < 29 \text{ mL/min}$ ) 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  $\leq$  ULN and AST  $>$  ULN) or (ULN  $<$  total bilirubin  $\leq 1.5 \times$  ULN)]. The effect of moderate (total bilirubin 1.5 to 3 times ULN) and severe (total bilirubin  $>$  3 times ULN) hepatic impairment on amivantamab pharmacokinetics is unknown.

#### 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 signaling 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  
24 months

### 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 (either 1,050 mg for patients < 80 kg or 1,400 mg for patients ≥ 80 kg) and the number of Rybrevant vials needed based on patient's baseline weight (see section 4.2). Each vial contains 350 mg of amivantamab.
- 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 micrometer). 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.
- 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.

### **7. MARKETING AUTHORISATION HOLDER**

Janssen-Cilag International NV  
Turnhoutseweg 30  
B-2340 Beerse  
Belgium

### **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/21/1594/001

### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

### **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **ANNEX II**

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE  
AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND  
USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE  
MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE  
AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**
- E. SPECIFIC OBLIGATION TO COMPLETE  
POST-AUTHORISATION MEASURES FOR THE CONDITIONAL  
MARKETING AUTHORISATION**

**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND  
MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer of the biological active substance

Janssen Sciences Ireland UC  
Barnahely  
Ringaskiddy, Co. Cork  
Ireland

Name and address of the manufacturer responsible for batch release

Janssen Biologics B.V.  
Einsteinweg 101  
2333 CB Leiden  
The Netherlands

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING  
AUTHORISATION**

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND  
EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.



**E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION**

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

<b>Description</b>	<b>Due date</b>
In order to further confirm the efficacy and safety of amivantamab in the treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations, the MAH should submit the results of study 61186372NSC3001, a randomised, open-label Phase 3 study comparing amivantamab in combination with carboplatin-pemetrexed therapy versus carboplatin-pemetrexed, in advanced or metastatic NSCLC patients with activating EGFR Exon 20 insertion mutations in the first-line setting.	31/03/2023

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Rybrevant 350 mg concentrate for solution for infusion  
amivantamab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One vial of 7 mL contains 350 mg of amivantamab (50 mg/mL).

**3. LIST OF EXCIPIENTS**

Excipients: ethylenediaminetetraacetic acid (EDTA), L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 80, sucrose, and water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Concentrate for solution for infusion  
1 vial

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For intravenous use after dilution.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Do not shake.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator.  
Do not freeze.  
Store in the original package in order to protect from light.

<b>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</b>
--

<b>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</b>
---

Janssen-Cilag International NV  
Turnhoutseweg 30  
B-2340 Beerse  
Belgium

<b>12. MARKETING AUTHORISATION NUMBER(S)</b>
--

EU/1/21/1594/001

<b>13. BATCH NUMBER</b>
-------------------------

Lot

<b>14. GENERAL CLASSIFICATION FOR SUPPLY</b>
--

<b>15. INSTRUCTIONS ON USE</b>
--------------------------------

<b>16. INFORMATION IN BRAILLE</b>
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Justification for not including Braille accepted.

<b>17. UNIQUE IDENTIFIER – 2D BARCODE</b>
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2D barcode carrying the unique identifier included.

<b>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</b>
--

PC  
SN  
NN

<b>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</b> <b>VIAL</b>
--

<b>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION</b>
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Rybrevant 350 mg sterile concentrate  
amivantamab  
IV

<b>2. METHOD OF ADMINISTRATION</b>
------------------------------------

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</b>
--

7 mL

<b>6. OTHER</b>
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## **B. PACKAGE LEAFLET**

## **Package leaflet: Information for the patient**

### **Rybrevent 350 mg concentrate for solution for infusion** amivantamab

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you are given this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Rybrevent is and what it is used for
2. What you need to know before you are given Rybrevent
3. How Rybrevent is given
4. Possible side effects
5. How to store Rybrevent
6. Contents of the pack and other information

## **1. What Rybrevent is and what it is used for**

### **What Rybrevent is**

Rybrevent is a cancer medicine. It contains the active substance ‘amivantamab’, which is an antibody (type of protein) designed to recognise and attach to specific targets in the body.

### **What Rybrevent is used for**

Rybrevent is used in adults with a type of lung cancer called ‘non-small cell lung cancer’. It is used when the cancer has spread to other parts of your body and has gone through certain changes (Exon 20 insertion mutations) in a gene called ‘EGFR’.

### **How Rybrevent works**

The active substance in Rybrevent, amivantamab, targets two proteins found on cancer cells:

- epidermal growth factor receptor (EGFR), and
- mesenchymal-epithelial transition factor (MET).

This medicine works by attaching to these proteins. This may help to slow or stop your lung cancer from growing. It may also help to reduce the size of the tumour.

## **2. What you need to know before you are given Rybrevent**

### **Do not use Rybrevent if**

- you are allergic to amivantamab or any of the other ingredients of this medicine (listed in section 6).

Do not use this medicine if the above applies to you. If you are not sure, talk to your doctor or nurse before you are given this medicine.

### **Warnings and precautions**

Tell your doctor or nurse before you are given Rybrevent if:

- you have suffered from inflammation of your lungs (a condition called ‘interstitial lung disease’ or ‘pneumonitis’).



**Tell your doctor or nurse straight away while taking this medicine if you get any of the following side effects (see section 4 for more information):**

- Any side effect while the medicine is being given into your vein.
- Sudden difficulty in breathing, cough, or fever that may suggest inflammation of the lungs.
- Skin problems. To reduce the risk of skin problems, keep out of the sun, wear protective clothing, apply sunscreen, and use moisturisers regularly on your skin and nails while taking this medicine. You will need to continue doing this for 2 months after you stop treatment.
- Eye problems. If you have vision problems or eye pain contact your doctor or nurse straight away. If you use contact lenses and have any new eye symptoms, stop using contact lenses and tell your doctor straight away.

### **Children and adolescents**

Do not give this medicine to children or young people below 18 years of age. This is because it is not known whether the medicine is safe and effective in this age group.

### **Other medicines and Rybrevant**

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

### **Contraception**

- If you could become pregnant, you must use effective contraception during Rybrevant treatment and for 3 months after stopping treatment.

### **Pregnancy**

- Tell your doctor or nurse before you are given this medicine if you are pregnant, think you might be pregnant, or are planning to have a baby.
- It is possible that this medicine may harm an unborn baby. If you become pregnant while being treated with this medicine, tell your doctor or nurse straight away. You and your doctor will decide if the benefit of having the medicine is greater than the risk to your unborn baby.

### **Breast-feeding**

It is not known if Rybrevant passes into breast milk. Ask your doctor for advice before being given this medicine. You and your doctor will decide if the benefit of breast-feeding is greater than the risk to your baby.

### **Driving and using machines**

If you feel tired, feel dizzy, or if your eyes are irritated or vision is affected after taking Rybrevant, do not drive or use machinery.

### **Rybrevant contains sodium**

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'. However, before Rybrevant is given to you, it may be mixed with a solution that contains sodium. Talk to your doctor if you are on a low salt diet.

## **3. How Rybrevant is given**

### **How much is given**

Your doctor will work out the correct dose of Rybrevant for you. The dose of this medicine will depend on your body weight at the start of your therapy.

The recommended dose of Rybrevant is:

- 1,050 mg if you weigh less than 80 kg.
- 1,400 mg if you weigh more than or equal to 80 kg.

**How the medicine is given**

This medicine will be given to you by a doctor or nurse. It is given as a drip into a vein ('intravenous infusion') over several hours.

Rybrevent is given as follows:

- once a week for the first 4 weeks
- then once every 2 weeks starting at week 5, for as long as you keep getting benefit from the treatment.

In the first week, your doctor will give you the Rybrevent dose split over two days.

**Medicines given during treatment with Rybrevent**

Before each infusion of Rybrevent, you will be given medicines which help lower the chance of infusion-related reactions. These may include:

- medicines for an allergic reaction (antihistamines)
- medicines for inflammation (corticosteroids)
- medicines for fever (such as paracetamol).

You may also be given additional medicines based on any symptoms you may experience.

**If you are given more Rybrevent than you should**

This medicine will be given by your doctor or nurse. In the unlikely event that you are given too much (an overdose), your doctor will check you for side effects.

**If you forget your appointment to have Rybrevent**

It is very important to go to all your appointments. If you miss an appointment, make another one as soon as possible.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

**4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Serious side effects**

Tell your doctor or nurse straight away if you notice the following serious side effects:

**Very common** (may affect more than 1 in 10 people):

- Signs of a reaction to the infusion - such as chills, feeling short of breath, feeling sick (nausea), flushing, chest discomfort, and vomiting while the medicine is being given. This can happen especially with the first dose. Your doctor may give you other medicines, or the infusion may need to be slowed down or stopped.
- Skin problems - such as rash (including acne), infected skin around the nails, dry skin, itching, pain, and redness. Tell your doctor if your skin or nail problems get worse.

**Common** (may affect up to 1 in 10 people):

- Eye problems - such as dry eye, swollen eyelid, itchy eyes, problems with vision, growth of eyelashes.
- Signs of an inflammation in the lungs - such as sudden difficulty in breathing, cough, or fever. This could lead to permanent damage ('interstitial lung disease'). Your doctor may wish to stop Rybrevent if you get this side effect.

**Uncommon** (may affect up to 1 in 100 people):

- inflamed cornea (front part of the eye)
- inflammation inside the eye that may affect vision

- life-threatening rash with blisters and peeling skin over much of the body (toxic epidermal necrolysis).

### **Other side effects**

Tell your doctor if you notice any of the following side effects:

**Very common** (may affect more than 1 in 10 people):

- low level of the protein 'albumin' in the blood
- swelling caused by fluid build up in the body
- feeling very tired
- sores in the mouth
- constipation or diarrhoea
- decreased appetite
- increased level of the liver enzyme 'alanine aminotransferase' in the blood, a possible sign of liver problems
- increased level of the enzyme 'aspartate aminotransferase' in the blood, a possible sign of liver problems
- feeling dizzy
- increased level of the enzyme 'alkaline phosphatase' in the blood
- muscle aches
- low level of calcium in the blood.

**Common** (may affect up to 1 in 10 people)

- stomach pain.

### **Reporting of side effects**

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

## **5. How to store Rybrevant**

Rybrevant will be stored at the hospital or clinic.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial label after "EXP". The expiry date refers to the last day of that month.

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.

Store in a refrigerator (2°C to 8°C). Do not freeze.

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

Medicines should not be disposed of via wastewater or household waste. Your healthcare professional will throw away any medicines that are no longer being used. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What Rybrevant contains

- The active substance is amivantamab. One mL of concentrate for solution for infusion contains 50 mg of amivantamab. One vial of 7 mL concentrate contains 350 mg of amivantamab.
- The other ingredients are ethylenediaminetetraacetic acid (EDTA), L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 80, sucrose, and water for injections (see section 2).

### What Rybrevant looks like and contents of the pack

Rybrevant is a concentrate for solution for infusion and is a colourless to pale yellow liquid. This medicine is available in a carton pack containing 1 glass vial of 7 mL of concentrate.

### Marketing Authorisation Holder

Janssen-Cilag International NV  
Turnhoutseweg 30  
B-2340 Beerse  
Belgium

### Manufacturer

Janssen Biologics B.V.  
Einsteinweg 101  
2333 CB Leiden  
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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**United Kingdom (Northern Ireland)**

Janssen Sciences Ireland UC  
Tel: +44 1 494 567 444

**This leaflet was last revised in.**

This medicine has been given 'conditional approval'.

This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.

**The following information is intended for healthcare professionals only:**

This medicinal product must not be mixed with other medicinal products except those mentioned below.

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

Preparation

- Determine the dose required (either 1,050 mg or 1,400 mg) and the number of Rybrevant vials needed based on patient's baseline weight. Each vial of Rybrevant contains 350 mg of amivantamab.
- 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 micrometer). 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.
- 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.

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.

#### **ANNEX IV**

#### **CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION PRESENTED BY THE EUROPEAN MEDICINES AGENCY**



**Conclusions presented by the European Medicines Agency on:**

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.