PROFESSIONAL INFORMATION

SCHEDULING STATUS

Schedule 4

1. NAME OF THE MEDICINE

RYBREVANT

350 mg concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 50 mg amivantamab.

Each 7 mL vial of concentrate for solution for infusion 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 (see section 5.1-Pharmacodynamic Properties - Mechanism of action).

Excipients with known effect

Contains sugar: Each 7 mL vial of concentrate for solution for infusion contains 595 mg of sucrose.

Contains sodium: Each 7 mL vial of concentrate for solution for infusion contains 0,017 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

RYBREVANT is colourless to pale yellow preservative-free liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

RYBREVANT should be administered by a healthcare professional with appropriate medical support to manage infusion-related reactions (IRRs) if they occur (see section 4.4).

Administer pre-infusion medications (see Pre-infusion medications).

When considering the use of RYBREVANT, EGFR Exon 20 insertion mutation presence should be established using a validated test (see section 5.1 - Pharmacodynamic Effects - Clinical studies).

Posology - adults (≥ 18 years)

The recommended dose of RYBREVANT is provided in Table 1, and the dosing schedule is provided in Table 2.

Table 1: Recommended Dose of RYBREVANT

Body Weight of Patient (at Baseline*)	Recommended Dose	Number of 350 mg/7 mL RYBREVANT 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

It is recommended that patients are treated with RYBREVANT until unacceptable toxicity or lack of clinical benefit.

Pre-infusion medications

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

Table 3: Pre-Medications

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

* Required at all doses.

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

Infusion Rates

Administer RYBREVANT infusion intravenously according to the infusion rates in Table 4. Due to the frequency of IRRs at the first dose, infusion via a peripheral vein at Week 1 and Week 2 should be considered to minimise medicine exposure in the event of an IRR; infusion via

central line may be administered for subsequent weeks. It is recommended for the first dose to be diluted as close to administration as possible to allow for maximal flexibility in IRR management.

Table 4: Infusion Rates for RYBREVANT Administration

1 050 mg Dose			
Week	**Dose (per 250 mL bag)**	**Initial Infusion Rate**	**Subsequent Infusion Rate†**
Week 1 (split dose infusion)			
Week 1 *Day 1*	350 mg	50 mL/hr	75 mL/hr
Week 1 *Day 2*	700 mg	50 mL/hr	75 mL/hr
Week 2	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**
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 infusion-related reactions.

Missed dose(s)

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

Dose modifications

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

Table 5: RYBREVANT Dose Reductions for Adverse Reactions

Body Weight at Baseline	Initial Dose	1st Dose Reduction	2nd Dose Reduction	3rd 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	

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

Table 6: RYBREVANT Dosage Modifications for Adverse Reactions

Adverse Reaction	**Severity**	**Dose Modification**
	Grade 1 to 3	• Interrupt infusion at the first sign of IRRs.

Infusion-Related Reactions (IRR) (see *section 4.4*)		• Additional supportive medications (e.g., additional glucocorticoids, antihistamine, antipyretics and antiemetics) should be administered as clinically indicated. • Upon resolution 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 4). • Pre-medications should be administered prior to the next dose.
	Recurrent Grade 3 or Grade 4	Permanently discontinue
Interstitial Lung Disease / Pneumonitis (see *section 4.4)*	Suspected ILD/ pneumonitis	Withhold
	Confirmed ILD/ pneumonitis	Permanently discontinue
Skin and Nail Reactions (see *section 4.4*)	Grade 2	• Supportive care should be initiated. • If there is no improvement after 2 weeks, consider reducing the dose (see Table 5).
	Grade 3	• Supportive care should be initiated.

		• Withhold until the adverse reaction improves to ≤ Grade 2 • Resume at reduced dose (see Table 5).
	Grade 4 (including severe bullous, blistering or exfoliating skin conditions)	Permanently discontinue
Other Adverse Reactions (see *section 4.8*)	Grade 3	• Withhold until adverse reaction improves to ≤ Grade 1 or baseline. • Resume at same dose if recovery occurs within 1 week. • Resume at reduced dose (see Table 5) if recovery occurs after 1 week. • Consider permanently discontinuing if recovery does not occur within 4 weeks.
	Grade 4	• Withhold until adverse reaction improves to ≤ Grade 1 or baseline. • Resume at reduced dose (see Table 5) if recovery occurs within 4 weeks. • Consider permanently discontinuing if recovery does not occur within 4 weeks.

Special populations

Paediatrics (17 years of age and younger)

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

Elderly (65 years of age and older)

Of the 362 patients treated with RYBREVANT in EDI1001, 41 % were 65 years of age or older, and 12 % were 75 years of age or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. No dosage adjustment is necessary (see 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 dosage adjustment is necessary for patients with mild or moderate renal impairment. No data are available in patients with severe renal impairment (see section 5.2).

Hepatic impairment

No formal studies of amivantamab in patients with hepatic impairment have been conducted. Based on population PK analyses, no dosage adjustment is necessary for patients with mild hepatic impairment. No data are available in patients with moderate or severe hepatic impairment (see *section 5.2*).

Method of administration

RYBREVANT solution must be diluted and prepared for intravenous infusion by a healthcare professional using aseptic technique. See section 6.6 for instructions on preparation and dilution.

1. Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0,2 micrometer). Administration sets must be made of either polyurethane (PU), polybutadiene (PBD), PVC, PP, or PE.
2. Do not infuse RYBREVANT concomitantly in the same intravenous line with other agents.
3. This medicinal product is for single use only. Any unused medicinal product should be disposed of in accordance with local requirements.

4.3 Contraindications

Hypersensitivity to amivantamab or to any of the excipients of RYBREVANT (see section 6.1).

4.4 Special warnings and precautions for use

The data described in this section reflects the safety profile of 380 patients with locally advanced or metastatic NSCLC who received 1 050 mg (for patients < 80 kg) or 1 400 mg (for patients ≥ 80 kg) of RYBREVANT monotherapy in Study EDI1001.

Infusion-related reactions

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

Prior to initial infusion (Week 1) of RYBREVANT, administer antihistamines, antipyretics, and glucocorticoids to reduce the risk of IRRs. For subsequent doses, administer antihistamines and antipyretics. Administer the initial infusion of RYBREVANT in split doses on Week 1, Days 1 and 2 (see section 4.2).

Treat patients with RYBREVANT in a setting with appropriate medical support necessary to treat IRRs. Interrupt RYBREVANT infusion at the first sign of IRRs and institute post-infusion medication as clinically indicated. Upon resolution of symptoms, resume the infusion at 50 % of the previous rate. For recurrent Grade 3 or 4 IRRs, permanently discontinue RYBREVANT (see section 4.2).

Interstitial lung disease

Interstitial lung disease (ILD) or ILD-like adverse reactions (e.g. pneumonitis) occurred in 2,6 % of patients treated with RYBREVANT. Patients with a medical history of ILD, medicine-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD have not been studied.

Monitor patients for symptoms indicative of ILD/pneumonitis (e.g., dyspnoea, cough, fever). If symptoms develop, interrupt treatment with RYBREVANT pending investigation of these

symptoms. Evaluate suspected ILD and initiate appropriate treatment as necessary. Discontinue RYBREVANT in patients with confirmed ILD (see section 4.2).

Skin and nail reactions

Rash (including dermatitis acneiform), pruritis and dry skin occurred in patients treated with RYBREVANT. Most cases were Grade 1 or 2, with Grade 3 events occurring in 3 % of patients. Rash leading to RYBREVANT discontinuation occurred in 0,3 % of patients. Rash usually developed within the first 4 weeks of therapy, with a median time to onset of 14 days. Nail toxicity occurred in patients treated with RYBREVANT. Most events were Grade 1 or 2, with Grade 3 nail toxicity occurring in 1,8 % of patients.

Toxic epidermal necrolysis (TEN) has been reported. Permanently discontinue RYBREVANT if TEN is confirmed.

Instruct patients to limit sun exposure during and for 2 months after RYBREVANT therapy. Protective clothing and use of sunscreen is advisable. Alcohol-free emollient cream is recommended for dry areas with the use of RYBREVANT. If skin or nail reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 or poorly-tolerated Grade 2 events, add systemic antibiotics and oral steroids and consider dermatologic consultation. Withhold, dose reduce, or permanently discontinue RYBREVANT based on severity (see section 4.2).

Eye disorders

Eye disorders, including keratitis (0,5 %), occurred in patients treated with RYBREVANT. Other reported adverse reactions included dry eye, blurred vision, eye pruritus, visual impairment, aberrant eyelash growth, ocular hyperaemia, conjunctival hyperaemia,

blepharitis and uveitis. All events were Grade 1-2. Refer patients presenting with worsening eye symptoms promptly to an ophthalmologist and advise discontinuation of contact lenses until symptoms are evaluated.

Sodium

This medicine contains less than 1 mmol sodium
(23 mg) per 7 mL, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

No medicine interaction studies have been performed.

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 childbearing potential / Contraception

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

Pregnancy

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

If the patient becomes pregnant while taking this medicine, the patient should be informed of the potential risk to the foetus.

Breastfeeding

It is not known whether RYBREVANT is excreted in human or animal milk or affects milk production. Because of the potential for serious adverse reactions from RYBREVANT in breast-fed infants, advise women not to breast-feed during treatment with RYBREVANT and for 3 months following the last dose of RYBREVANT.

Fertility

No data are available to determine potential effects of RYBREVANT on fertility in males or females.

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

The safety of RYBREVANT was evaluated in Study EDI1001, which included 380 patients with locally advanced or metastatic NSCLC after failure of platinum-based chemotherapy. Patients received RYBREVANT 1 050 mg (for patients < 80 kg) or 1 400 mg (for patients ≥ 80 kg) by intravenous infusion once weekly for 4 weeks, then every 2 weeks starting at Week 5 until disease progression or unacceptable toxicity. The median treatment duration was 4,1 months (range: 0,0 to 39,7 months).

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

Table 7 presents adverse reactions reported in patients treated with RYBREVANT in Study EDI1001.

Tabulated list of adverse reactions

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

Table 7: Adverse reactions in Patients with NSCLC with Exon 20 Insertion Mutations in Study EDI1001 Treated with RYBREVANT (N=380)

System Organ Class Adverse Reaction	**Frequency** **(all grades)**	**All Grades** **(%)**	**Grade 3-4** **(%)**
Skin and subcutaneous tissue disorders			
Rash [a]	Very common	76	3
Nail toxicity [b]	Very common	47	2
Dry skin [c]	Very common	19	0
Pruritus	Very common	18	0
Toxic epidermal necrolysis	Uncommon	0,3	0,3
Injury, poisoning and procedural complications			
Infusion-related reaction	Very common	67	2
Gastrointestinal disorders			
Stomatitis [d]	Very common	24	0,5
Nausea	Very common	23	0,5
Constipation	Very common	23	0
Vomiting	Very common	12	0,5
Diarrhoea	Very common	11	2
Abdominal pain [e]	Common	9	0,8
Metabolism and nutrition disorders			
Hypoalbuminaemia [f]	Very common	31	2
Decreased appetite	Very common	16	0,5
Hypocalcaemia	Very common	10	0,3
Hypokalaemia	Common	9	2

System Organ Class Adverse Reaction	Frequency (all grades)	All Grades (%)	Grade 3-4 (%)
Hypomagnesaemia	Common	8	0
General disorders and administration site conditions			
Oedema [g]	Very common	26	0,8
Fatigue [h]	Very common	26	0,8
Investigations			
Alanine aminotransferase increased	Very common	15	2
Aspartate aminotransferase increased	Very common	13	1
Blood alkaline phosphatase increased	Very common	12	0,5
Nervous system disorders			
Dizziness [i]	Very common	13	0,3
Musculoskeletal and connective tissue disorders			
Myalgia	Very common	11	0,3
Eye disorders			
Other eye disorders [j]	Common	6	0
Visual impairment [k]	Common	3	0
Growth of eyelashes [l]	Common	1	0
Keratitis	Uncommon	0,5	0
Uveitis	Uncommon	0,3	0
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease [m]	Common	3	0,5

[a] 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

[b] Nail toxicity: ingrowing nail, nail bed infection, nail cuticle fissure, nail disorder, nail ridging, onychoclasis, onycholysis, paronychia

[c] Dry skin: dry skin, eczema, eczema asteatotic, skin fissures, xeroderma

[d] Stomatitis: aphthous ulcer, cheilitis, glossitis, lip ulceration, mouth ulceration, mucosal inflammation, stomatitis

[e] Abdominal pain: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, epigastric discomfort, gastrointestinal pain

[f] Hypoalbuminaemia: blood albumin decreased, hypoalbuminaemia

[g] Oedema: eye oedema, eyelid oedema, face oedema, generalised oedema, localised oedema, oedema, oedema peripheral, periorbital oedema, peripheral swelling, swelling face

[h] Fatigue: asthenia, fatigue

[i] Dizziness: dizziness, dizziness exertional, vertigo

[j] Other eye disorders: blepharitis, conjunctival hyperaemia, corneal irritation, dry eye, episcleritis, eye disorder, eye pruritus, noninfective conjunctivitis, ocular hyperaemia

[k] Visual impairment: vision blurred, visual acuity reduced, visual impairment

[l] Growth of eyelashes: growth of eyelashes, trichomegaly

[m] Interstitial lung disease: interstitial lung disease, pneumonitis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions via "**6.04 Adverse Drug Reaction Reporting Form**" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/index/8

Alternatively, suspected adverse reactions may be reported directly to Janssen Pharmaceutica (see section 7 for contact details or visit www.janssen.com).

4.9 Overdose

Symptoms and signs

There is no information on overdosage with RYBREVANT.

Treatment

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 30.2 Antibodies

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 and resistance EGFR mutations and MET mutations and amplifications. Amivantamab binds to the extracellular domains of EGFR and MET.

Preclinical studies show amivantamab is active against tumours with primary EGFR activating mutations such as Exon 19 deletions, L858R substitution, and Exon 20 insertion mutations; secondary EGFR resistance mutations such as T790M and C797S; and resistance to EGFR inhibition due to activation of the MET pathway. Amivantamab disrupts EGFR and MET 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; thereafter, albumin concentration stabilised for the remainder of amivantamab treatment.

Immunogenicity

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

Clinical efficacy and safety

EDI1001 (CHRYSALIS) is a multicenter, open-label, multi-cohort study conducted to assess the safety and efficacy of RYBREVANT in subjects with locally advanced or metastatic NSCLC. Efficacy was evaluated in 114 subjects with locally advanced or metastatic NSCLC who had EGFR Exon 20 insertion mutations as determined by previous local standard of care testing, whose disease had progressed on or after platinum-based chemotherapy, and who had median follow-up of 12,5 months. RYBREVANT was administered intravenously at 1050 mg for subjects < 80 kg or 1400 mg for subjects ≥ 80 kg once weekly for 4 weeks, then every 2 weeks starting at Week 5 until disease progression or unacceptable toxicity.

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

Efficacy results are summarised in Table 8.

Table 8: Efficacy Results for EDI1001 (CHRYSALIS)

	BICR Assessment (N=114)	**Investigator Assessment (N=114)**
Overall Response Rate[a,b] (95 % CI)	43 % (34 %, 53 %)	37 % (28 %, 46 %)
Complete response	3 %	0 %
Partial response	40 %	37 %
Clinical Benefit Rate[a,c] (95 % CI)	74 % (65 %, 82 %)	75 % (67 %, 83 %)
Duration of Response[a] **(DOR)**		

Median (95 % CI), months[d]	10,8 (6,9; 15,0)	12,5 (6,5; 16,1)
Patients with DOR ≥ 6 months	55 %	64 %
Median Progression-Free Survival[a] (95 % CI), months	6,7 (5,5; 9,7)	6,9 (5,6; 8,6)
Median Time to Treatment Failure (95 % CI), months	8,1 (6,7; 10,6)	
Median Overall Survival (95 % CI), months	22,8 (17,5; NE)	

BICR=Blinded Independent Central Review; NE=Not Estimable

[a] by RECIST v1.1

[b] Confirmed response.

[c] Clinical benefit rate is defined as complete response + partial response + stable disease (duration of at least 11 weeks).

[d] Based on Kaplan-Meier estimate

Anti-tumour activity was observed across studied mutation subtypes

5.2 Pharmacokinetic properties

Amivantamab area under the concentration-time curve (AUC_{1week}) increases proportionally over a dose range from 350 to 1 750 mg (0,33 to 1,67 times the recommended dose for subjects < 80 kg and 0,25 to 1,25 times the recommended dose for subjects ≥ 80 kg).

Following administration of RYBREVANT at the recommended dose and schedule, the mean ± SD serum maximal concentration (C_{max}) was 836 ± 264 mcg/mL at 1 050 mg for subjects < 80 kg and 655 ± 109 mcg/mL at 1 400 mg for subjects ≥ 80 kg at the end of weekly dosing following the fifth dose. The mean ± SD AUC_{1week} following the fifth dose was 94,946 ± 35,440 mcg.h/mL at 1 050 mg for subjects < 80 kg and 76,946 ± 14,557 mcg.h/mL at 1400

mg for subjects ≥ 80 kg. The mean serum AUC_{1week} was approximately 2,9-fold higher after the fifth dose following the weekly dosing compared to the first dose.

When RYBREVANT was administered, amivantamab steady state was achieved approximately 2 months into the every 2-week dosing period (by the ninth infusion) at 1 050 mg, and amivantamab mean ± SD ratio of AUC_{1week} at steady state to AUC_{1week} after the first dose was 2,44 ± 0,54.

Distribution

Amivantamab mean ± SD volume of distribution estimated from population PK parameters was 5,13 ± 1,78 L following administration of the recommended dose of RYBREVANT.

Elimination

Amivantamab clearance decreased with increasing dose and with multiple dosing. The mean ± SD linear clearance was estimated to be 360 ± 144 mL/day and the mean ± SD estimated terminal half-life associated with linear clearance estimated from population PK parameter estimates was 11,3 ± 4,53 days following administration of the recommended dose of RYBREVANT.

Special populations

Paediatrics (17 years of age and younger)

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

Elderly (65 years of age and older)

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

Renal impairment

No clinically meaningful effect on the pharmacokinetics of amivantamab was observed in patients with mild (60 ≤ 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.

Gender

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

Weight

The central volume of distribution and clearance of amivantamab increased with increasing body weight. Similar amivantamab exposures were achieved at the recommended dose of

RYBREVANT in patients with a body weight < 80 kg who received 1 050 mg and patients with a body weight ≥ 80 kg who received 1 400 mg.

5.3 Preclinical safety data

In repeat-dose toxicity studies in cynomolgus monkeys, amivantamab was well-tolerated at weekly doses up to 120 mg/kg intravenously for 6 weeks or 3 months (~6-8 x C_{max} and ~5-7x AUC human exposure for 1 050 and 1 400 mg intravenous doses). There were no effects on cardiovascular, respiratory, and nervous system function. Clinical pathology demonstrated non-adverse elevations in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and globulins, and non-adverse decreases in albumin when compared to the control group. All these values returned to normal ranges in recovery groups. A subcutaneous local tolerance study showed that amivantamab was well tolerated at injection sites in cynomolgus monkeys administered two 125 mg/kg weekly doses.

Carcinogenicity and Mutagenicity

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

Reproductive Toxicology

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethylenediaminetetraacetic acid (EDTA) disodium salt dihydrate

L-Histidine

L-Histidine hydrochloride monohydrate

L-Methionine

Polysorbate 80

Sucrose

Water for Injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 4.2

6.3 Shelf life

Unopened vial

18 months

See expiry date on the outer pack.

After dilution:

Since amivantamab solutions do not contain a preservative, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used

immediately. Administer diluted solutions within 10 hours (including infusion time) at room temperature (15 °C to 25 °C) and in room light.

6.4 Special precautions for storage

Store RYBREVANT in a refrigerator (2 °C – 8 °C).

Do not freeze.

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

For storage conditions after dilution of the medicine, see Section 6.3.

6.5 Nature and contents of container

Each 7 mL concentrate for solution for infusion is packed in a Type 1 glass vial with an elastomeric closure and a silver coloured aluminium seal with a white flip-off cap containing 350 mg amivantamab. Pack size of 1 vial.

The RYBREVANT vial is packed into an opaque paperboard carton. Each carton consists of one single-use vial and a package leaflet.

6.6 Special precautions for disposal and other handling

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

1. Determine the dose required (either 1 050 mg or 1 400 mg) and number of RYBREVANT vials needed based on patient's baseline weight (see section 4.2). Each vial of RYBREVANT contains 350 mg of amivantamab.

2. Check that the RYBREVANT solution is colourless to pale yellow. Do not use if discolouration or visible particles are present.
3. Withdraw and then discard a volume of either 5 % dextrose [glucose] solution or 0,9 % sodium chloride solution from the 250 mL infusion bag equal to the volume of RYBREVANT to be added (i.e., discard 7 mL diluent from the infusion bag for each RYBREVANT vial). Infusion bags must be made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE), or polyolefin blend (PP+PE).
4. Withdraw 7 mL of RYBREVANT from each vial and add it to the infusion bag. The final volume in the infusion bag should be 250 mL. Each vial contains a 0,5 mL overfill to ensure sufficient extractable volume. Discard any unused portion left in the vial.
5. Gently invert the bag to mix the solution. Do not shake.
6. Visually inspect the diluted solution before administration. Do not use if discolouration or visible particles are observed.
7. Diluted solutions should be administered within 10 hours (including infusion time) at room temperature (15 °C to 25 °C) and in room light.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

57/30.2/0435

9 DATE OF FIRST AUTHORISATION

Date of registration: 3 September 2024