▼This medicine is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

RYBREVANT® (amivantamab)

concentrate for solution for infusion

1. NAME OF THE MEDICINE

Amivantamab

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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 Mechanism of action).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (injection).

RYBREVANT is available as a colourless to pale yellow preservative-free liquid concentrate for intravenous infusion after dilution.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

RYBREVANT has **provisional approval** for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that has an activating epidermal-growth factor receptor (EGFR) exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy.

The decision to approve this indication has been made on the basis of objective response rate and duration of response in a single arm study. Continued approval of this indication depends on verification and description of benefit in a confirmatory study.

4.2 DOSE AND METHOD OF ADMINISTRATION

RYBREVANT should be administered by a healthcare professional in a setting with appropriate medical support for the management of infusion-related reactions (IRRs), including equipment for cardiorespiratory resuscitation. See Section 4.4 Special warnings and precautions for use.

Administer pre-infusion medications (see Section 4.2 Pre-infusion medications).

When considering the use of RYBREVANT, the presence of an EGFR exon 20 insertion mutation should be established using a validated test (see Section 5.1 Clinical trials).

Dosage

Dosage – adults (≥18 years)

The recommended dose of RYBREVANT is provided in Table 1, and the dosing schedule is provided in Table 2. (See also Infusion rates – Table 4). Administer RYBREVANT until disease progression or unacceptable toxicity.

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	1050 mg	3
Greater than or equal to 80 kg	1400 mg	4

* Dose adjustments not required for subsequent body weight changes.

Table 2: Dosing schedule for RYBREVANT

Weeks	**Schedule**
Week 1	Split dose over two infusions: one on Day 1 and one on Day 2
Weeks 2 to 4	Full dose infusion on Day 1 of each week
Week 5 onwards	Full dose infusion once every 2 weeks (starting with a dose in Week 5)

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 summarises the recommendations regarding pre-infusion medications.

Table 3: Pre-infusion 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 (500 to 1,000 mg)	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 into a peripheral vein should be considered in Week 1 and Week 2 to minimise drug exposure in the event of an IRR; a central line may be used subsequently. Particularly for the first dose, prepare the dilution for infusion as close as possible to the time of administration, to allow for maximal flexibility in IRR management.

Table 4: Infusion rates for RYBREVANT administration

1050 mg dose			
Week	**Dose (per 250 mL bag)**	**Initial infusion rate**	**Subsequent infusion rate**[†]
Week 1 (split dose infusion)			
Week 1 *Day 1*	350 mg	50 mL/hr	75 mL/hr
Week 1 *Day 2*	700 mg	50 mL/hr	75 mL/hr
Week 2	1050 mg	85 mL/hr	
Week 3	1050 mg	125 mL/hr	
Week 4	1050 mg	125 mL/hr	
Subsequent weeks[*]	1050 mg	125 mL/hr	
1400 mg dose			
Week	**Dose (per 250 mL bag)**	**Initial infusion rate**	**Subsequent infusion rate**[†]
Week 1 (split dose infusion)			
Week 1 *Day 1*	350 mg	50 mL/hr	75 mL/hr
Week 1 *Day 2*	1050 mg	35 mL/hr	50 mL/hr
Week 2	1400 mg	65 mL/hr	
Week 3	1400 mg	85 mL/hr	
Week 4	1400 mg	125 mL/hr	
Subsequent weeks[*]	1400 mg	125 mL/hr	

[*] Starting at Week 5, patients are dosed every 2 weeks.
[†] Increase the initial infusion rate to the subsequent infusion rate after 2 hours in the absence of infusion-related reactions.

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	1050 mg	700 mg	350 mg	Discontinue RYBREVANT
Greater than or equal to 80 kg	1400 mg	1050 mg	700 mg	

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

Table 6: RYBREVANT dosage modifications for adverse reactions

Adverse reaction	Severity	Dose modification
Infusion-related reactions (IRR) (see section 4.4)	Grade 1 to 3	• Interrupt infusion at the first sign of IRRs • Give supportive medications (e.g., additional glucocorticoids, antihistamine, antipyretics and antiemetics) 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 instructions in Table 4 • Administer pre-medications prior to 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	• Initiate supportive care • If there is no improvement after 2 weeks, consider reducing the dose (see Table 5)
	Grade 3	• Initiate supportive care • Withhold until the adverse reaction improves to ≤ Grade 2 • Resume at reduced dose (see Table 5) • If no improvement within 2 weeks, permanently discontinue
	Grade 4 (including severe bullous, blistering or exfoliating skin conditions such as toxic epidermal necrolysis (TEN))	Permanently discontinue

Adverse reaction	Severity	Dose modification
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 • Permanently discontinue 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 • Permanently discontinue if recovery does not occur within 4 weeks • Permanently discontinue for recurrent Grade 4 reactions

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 Study EDI1001 (also known as CHRYSALIS), 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 Pharmacokinetic properties).

Renal impairment

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

Hepatic impairment

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

Administration

Preparation for administration

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

1. Determine the dose required (either 1050 mg or 1400 mg) and number of RYBREVANT vials needed based on patient's baseline weight (see Table 1). Each vial of RYBREVANT contains 350 mg of amivantamab.
2. Check that the RYBREVANT solution is colourless to pale yellow. Do not use if discoloration or visible particles are present.

3. Withdraw and then discard a volume of either 5% dextrose [glucose] solution or 0.9% sodium chloride solution from the 250 mL infusion bag equal to the volume of RYBREVANT to be added (i.e., discard 7 mL diluent from the infusion bag for each RYBREVANT vial). Infusion bags must be made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE), or polyolefin blend (PP+PE).
4. Withdraw 7 mL of RYBREVANT 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.

Administration

1. Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.2 micrometer). Administration sets must be made of either polyurethane (PU), polybutadiene (PBD), PVC, PP, or PE.
2. Do not infuse RYBREVANT concomitantly in the same intravenous line with other agents.
3. Product is for single use in one patient only. Discard any residue.

4.3 CONTRAINDICATIONS

Hypersensitivity to amivantamab or to any of the excipients listed in section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The data described in Special Warnings and Precautions for Use reflects exposure to RYBREVANT as a single agent in 380 patients with locally advanced or metastatic NSCLC who received a dose of 1050 mg (for patients <80 kg) or 1400 mg (for patients ≥80 kg) in Study EDI1001.

Infusion-related reactions

Infusion-related reactions (IRRs) were reported in 67% of patients treated with RYBREVANT, of which 98% were Grade 1-2, and 99% occurred at the first infusion with a median time to onset of 60 minutes. Signs and symptoms of IRR include dyspnoea, flushing, fever, chills, chest discomfort, hypotension, nausea and vomiting.

To reduce the risk of IRRs, premedicate with antihistamines, antipyretics, and glucocorticoids, and follow the infusion recommendations in Section 4.2 Dose and method of administration.

Give RYBREVANT infusions in a monitored setting with appropriate medical support for the treatment of IRRs, including cardiopulmonary resuscitation medication and equipment. Interrupt infusion if IRR is suspected, and reduce infusion rate or permanently discontinue RYBREVANT based on severity (see Section 4.2 Dose and method of administration, Table 6).

Interstitial lung disease/pneumonitis

Interstitial lung disease (ILD)/pneumonitis occurred in 2.6% of patients treated with RYBREVANT. Patients with a medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD were not included in the study.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnoea, cough, fever). Immediately withhold RYBREVANT in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed (see Section 4.2 Dose and method of administration, Table 6).

Skin and nail reactions

Rash (including dermatitis acneiform), pruritis and dry skin occurred in patients treated with RYBREVANT. Rash occurred in 76% of patients. 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) occurred in one patient (0.3%). 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 skin. 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 dermatology consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce, or permanently discontinue RYBREVANT based on severity (see Section 4.2 Dose and method of administration, Table 6).

Ocular toxicity

Eye disorders, including keratitis (0.5%) and uveitis (0.3%) 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 and blepharitis. 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. Withhold, dose reduce, or permanently discontinue RYBREVANT based on severity (see Section 4.2 Dose and method of administration, Table 6).

Use in the elderly

See section 4.2.

Paediatric use

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

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug interaction studies have been performed.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effect of amivantamab on fertility has not been studied.

Use in pregnancy – Pregnancy Category D

Based on its mechanism of action and findings in animal studies, amivantamab could cause fetal harm if administered to a pregnant patient. Whilst the use of amivantamab during pregnancy has not been studied, administration of other EGFR or MET inhibitor molecules to pregnant animals has resulted in an increased incidence of impairment of embryo-fetal development, embryolethality, and abortion. Human IgG1 is known to cross the placenta; therefore, amivantamab has the potential to be transmitted from a pregnant patient to the developing fetus. Advise patients of the potential risk to a fetus. Advise female patients of reproductive potential to use effective contraception (such as condoms) during treatment and for 3 months after the last dose of RYBREVANT. Advise male patients not to donate or store semen and to use effective contraception during treatment and for 3 months after the last dose of RYBREVANT.

Use in lactation

It is not known whether amivantamab is excreted in milk or affects milk production. Because of the potential for serious adverse reactions from RYBREVANT in a breastfed child, advise patients not to breastfeed during treatment with RYBREVANT and for 3 months following the last dose of RYBREVANT.

4.7 EFFECTS OF ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial data

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of RYBREVANT was evaluated in Study EDI1001, which included 153 patients with locally advanced or metastatic NSCLC with EGFR exon 20 mutations whose disease had progressed on or after platinum-based chemotherapy (see 5.1 Clinical trials). Patients received RYBREVANT 1050 mg (for patients < 80 kg) or 1400 mg (for patients ≥80 kg) by intravenous infusion once weekly for 4 weeks, then every 2 weeks starting at Week 5 until disease progression or unacceptable toxicity. The median treatment duration was 5.6 months (range: 0.0 to 23.9 months): 46% of patients were exposed for 6 months or longer and 22% were exposed for longer than a year.

The most common adverse reactions (≥20% incidence) were rash, IRR, nail toxicity, hypoalbuminaemia, fatigue, oedema, stomatitis, nausea, constipation, dry skin, and alanine aminotransferase increased. Serious adverse reactions in >1% of patients included ILD, diarrhoea, IRR, and rash. Five percent of patients discontinued RYBREVANT due to adverse reactions. The most frequent adverse reactions leading to treatment discontinuation were IRR and ILD.

Table 7: Adverse reactions (≥10%) in patients with NSCLC with exon 20 insertion mutations whose disease had progressed on or after platinum-based chemotherapy and received RYBREVANT in Study EDI1001 (N=153)

System Organ Class Adverse Reaction	**Frequency Category**	**All Grades (%)**	**Grade 3-4 (%)**
Skin and subcutaneous tissue disorders			
Rash[a]	Very common	85	4
Nail toxicity[b]	Very common	56	3
Dry skin[c]	Very common	23	0
Pruritus	Very common	16	0
Gastrointestinal disorders			
Stomatitis[d]	Very common	28	0.7
Nausea	Very common	25	0.7
Constipation	Very common	24	0
Diarrhoea	Very common	14	3
Vomiting	Very common	14	0.7
Abdominal pain[e]	Very common	11	0.7
Injury, poisoning and procedural complications			
Infusion-related reaction	Very common	63	3
Metabolism and nutrition disorders			
Decreased appetite	Very common	18	0.7
General disorders and administration site conditions			
Fatigue[f]	Very common	33	2
Oedema[g]	Very common	29	0.7
Pyrexia	Very common	17	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain[h]	Very common	48	0
Nervous system disorders			
Dizziness[i]	Very common	12	0.7
Peripheral neuropathy[j]	Very common	12	0
Headache[k]	Very common	10	0.7
Vascular disorders			
Haemorrhage[l]	Very common	24	0
Infections and infestations			
Pneumonia[m]	Very common	11	2.6

[a] Rash: acne, dermatitis, dermatitis acneiform, erythema, folliculitis, palmar-plantar erythrodysaesthesia syndrome, perineal rash, pustule, rash, rash erythematous, rash maculo-papular, rash general, rash pustular, rash vesicular, skin exfoliation, skin lesion

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

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

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

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

[f] Fatigue: asthenia, fatigue

[g] Oedema: eyelid oedema, face oedema, generalized oedema, oedema, oedema peripheral, periorbital oedema, periorbital swelling, peripheral swelling, swelling face

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

[i] Dizziness

[j] Peripheral neuropathy: hypoaesthesia, neuralgia, neuritis, paraesthesia, peripheral sensory neuropathy

[k] Headache: headache, migraine

[l] Haemorrhage: epistaxis, gastric haemorrhage, gingival bleeding, haematuria, haemoptysis, haemorrhage, mouth haemorrhage, mucosal haemorrhage

[m] Pneumonia: pneumonia, pneumonia aspiration, pulmonary sepsis

Clinically relevant adverse reactions that occurred in <10% of RYBREVANT-treated patients with NSCLC exon 20 insertion mutations in Study EDI1001 included those summarised in Table 8.

Table 8: Clinically relevant adverse reactions (<10%) in patients with NSCLC with exon 20 insertion mutations whose disease had progressed on or after platinum-based chemotherapy and who received RYBREVANT in Study EDI1001 (N=153)

System Organ Class Adverse Reaction	**Frequency Category**	**All Grades (%)**	**Grade 3-4 (%)**
Gastrointestinal disorders			
Abdominal pain[a]	Common	9	0.7
Eye disorders			
Other eye disorders[b]	Common	6	0
Visual impairment[c]	Common	2	0
Growth of eyelashes[d]	Common	1	0
Keratitis	Common	1	0
Uveitis	Uncommon	0.7	0
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease[e]	Common	4	0.7
Skin and subcutaneous tissue disorders			
Toxic epidermal necrolysis	Uncommon	0.7	0.7

[a] Abdominal pain: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, epigastric discomfort

[b] Other eye disorders: blepharitis, conjunctival hyperaemia, corneal irritation, dry eye, episcleritis, eye pruritus, ocular hyperaemia

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

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

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

Laboratory abnormalities

Table 9: Select laboratory abnormalities that worsened from baseline in at least 20% of patients with metastatic NSCLC with EGFR exon 20 insertion mutations whose disease had progressed on or after platinum-based chemotherapy and who received RYBREVANT in Study EDI1001

Laboratory abnormality	**RYBREVANT[+] (N=153)**	
	All Grades (%)	**Grades 3 or 4 (%)**
Chemistry		
Decreased albumin	83	8
Increased glucose	56	4
Increased alkaline phosphatase	52	5
Increased creatinine	48	0
Increased alanine aminotransferase	40	2
Decreased phosphate	36	7
Increased aspartate aminotransferase	34	1
Increased gamma-glutamyl transferase	29	4
Decreased magnesium	28	0
Decreased potassium	28	5
Decreased sodium	25	3
Decreased calcium	21	1
Hematology		
Decreased lymphocytes	38	7

[+] The denominator used to calculate the rate was the number of patients with a baseline value and at least one post-treatment value.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no information on overdosage with RYBREVANT.

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.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

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

In preclinical studies, amivantamab disrupted EGFR and MET signalling functions through blocking ligand binding and, in exon 20 insertion mutation models, enhancing degradation of EGFR and MET. 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

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 patients who received RYBREVANT and were evaluable for the presence of anti-drug antibodies tested positive for anti-amivantamab antibodies: one at 27 days, one at 59 days and one at 168 days after the first dose: all with titers of 1:40 or less. There are insufficient data to evaluate the effect of anti-drug antibodies on the pharmacokinetics, efficacy, or safety of RYBREVANT.

Clinical trials

Locally advanced or metastatic NSCLC with exon 20 insertion mutations

The efficacy and safety of amivantamab were evaluated in Study EDI1001: a multicentre, open-label, multi-cohort study conducted in patients with locally advanced or metastatic NSCLC. Efficacy was evaluated in 81 subjects 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 14.5 months. Identification of an EGFR exon 20 insertion mutation was determined by prospective local testing using tumour tissue (94%) or plasma (6%) samples. Patients with untreated brain metastases and patients with a history of ILD requiring

treatment with prolonged steroids or other immunosuppressive agents within the last 2 years were not eligible for the study.

Amivantamab was administered intravenously at a dose of 1050 mg (for patients <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 primary efficacy endpoint was overall response rate (ORR), defined as confirmed complete response (CR) or partial response (PR) based on RECIST v1.1, assessed by a blinded independent central review (BICR). Secondary efficacy endpoints included duration of response (DOR) according to BICR.

The median age amongst the 81 patients in the efficacy population was 62 (range: 42–84) years, with 9% of the patients ≥75 years of age; 59% were female; 49% were Asian and 37% were Caucasian; 74% had baseline body weight <80 kg; 95% had adenocarcinoma; and 46% had received prior immunotherapy. The median number of prior therapies was 2 (range: 1 to 7). At baseline, 32% had Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 67% had ECOG performance status of 1; 53% had never smoked; all patients had metastatic disease; and 22% had previous treatment for brain metastases.

Efficacy results are summarised in Table 10.

Table 10: Efficacy results in Study EDI1001

	Patients with EGFR exon 20 insertion-positive NSCLC previously treated with platinum-based chemotherapy (N=81)
Overall response rate[a] (95% CI)	43% (32%, 55%)
Complete response (CR) rate	4%
Partial response (PR) rate	40%
Duration of response[a]	
Median (95% CI), months	11.0 (6.9, NE)
Patients with DOR ≥ 6 months	60%

CI = confidence interval; NE = not estimable

[a] Kaplan-Meier estimates, based on confirmed responses

Of the 81 patients with EGFR exon 20 insertion mutations according to local testing, plasma samples from 96% of patients were tested retrospectively using Guardant360® CDx (3.7% did not have plasma samples for testing). EGFR exon 20 insertion mutations were not identified on the Guardant360® CDx test for 20% of patients. For the 76% of patients in whom exon 20 insertion mutations were identified, the variants identified were A767 (23%), S768 (16%), D770 (11%), N771 (11%), H773 (9%), P772 (3%), V769 (1%) and A763 (1%). There were no mutation variants identified amongst the efficacy population that were associated with an absence of confirmed responses.

5.2 PHARMACOKINETIC PROPERTIES

Amivantamab exposure increases proportionally over a dose range from 350 to 1750 mg (0.33 to 1.67 times the recommended dose for subjects <80 kg, and 0.25 to 1.25 times the recommended dose for subjects ≥ 80 kg).

Following administration of RYBREVANT at the recommended dose and schedule, following the fifth dose, the mean (±SD) maximal serum concentration (C_{max}) was 836 (±264) mcg/mL at 1050 mg for subjects <80 kg and 655 (±109) mcg/mL at 1400 mg for subjects ≥80 kg. The mean (±SD)

area under the concentration-time curve (AUC_{1week}) following the fifth dose was 94,946 (±35,440) mcg.h/mL at 1050 mg for subjects <80 kg and 76,946 (±14,557) mcg.h/mL at 1400 mg for subjects ≥80 kg.
Steady state amivantamab concentration was reached by the ninth infusion, and the accumulation ratio at steady state was 2.4.

Distribution

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

Excretion

The mean (±SD) clearance of amivantamab is 360 (±144) mL/day and the mean (±SD) terminal half-life is 11.3 (±4.5) days.

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 (creatinine clearance [CrCl] of 60 to <90 mL/min) and moderate (CrCl of 29 to <60 mL/min) renal impairment. The effect of severe renal impairment or end stage renal failure (CrCl <29 mL/min) on amivantamab pharmacokinetics is unknown.

Hepatic impairment

No clinically meaningful effect on 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. Changes in hepatic function are not expected to affect amivantamab elimination since IgG1-based molecules are not metabolised through hepatic pathways.

Sex

Amivantamab clearance was 24% higher in males than in females, but no clinically meaningful pharmacokinetic differences were observed between male and female patients.

Weight

The central volume of distribution and clearance of amivantamab increased with increasing body weight. Amivantamab exposure was 30-40% lower in patients who weighed ≥80 kg compared to patients with body weight <80 kg at the same dose. Similar amivantamab exposures were achieved at the recommended dose of RYBREVANT in patients with a body weight <80 kg who received 1050 mg and patients with a body weight ≥80 kg who received 1400 mg.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

As amivantamab is a monoclonal antibody, genotoxicity studies have not been conducted. Large protein molecules are not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

As amivantamab is a monoclonal antibody, carcinogenicity studies have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Disodium edetate
Histidine
Histidine hydrochloride monohydrate
Methionine
Polysorbate 80
Sucrose
Water for injections

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 4.2 Dose and Method of administration.

6.3 SHELF LIFE

Unopened vials

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

After dilution:

Since amivantamab solutions do not contain a preservative, 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 in a refrigerator at 2°C to 8°C.
Do not freeze.
Store in the original package in order to protect from light.
For storage conditions after dilution of the medicinal product, see Section 6.3 Shelf life.

6.5 NATURE AND CONTENTS OF CONTAINER

Type 1 glass vial with butyl rubber elastomer stopper and aluminium seal with a flip-off cap.

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

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE (POISON STANDARD)

S4 Prescription Medicine

SPONSOR

Janssen-Cilag Pty Ltd
1-5 Khartoum Road,
Macquarie Park,
NSW, 2113, AUSTRALIA
Telephone: 1800 226 334

8. DATE OF FIRST APPROVAL

01 Dec 2022

9. DATE OF REVISION

N/A

Summary table of changes

Section changed	Summary of new information
N/A	N/A