Product Monograph

Including Patient Medication Information

PrRYBREVANT®

amivantamab for injection

amivantamab is produced in mammalian cells using recombinant DNA technology

Concentrate for Solution for Intravenous Infusion

350 mg / 7 mL (50 mg/mL) single-use vial

Antineoplastic, monoclonal antibody

ATC code: L01FX18

PrRYBREVANT, indicated:

- for the treatment of adult 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,

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for RYBREVANT please refer to Health Canada's Notice of Compliance with conditions - drug products web site.

RYBREVANT, indicated:

- in combination with carboplatin and pemetrexed for the treatment of patients with locally advanced (not amenable to curative therapy) or metastatic NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations, whose disease has progressed on or after treatment with osimertinib,
- in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) with activating epidermal-growth factor receptor (EGFR) Exon 20 insertion mutations,

have been issued a market authorization **without conditions**.

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*a Johnson & Johnson company

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

Recent Major Label Changes

1 Indications	01/2025
4 Dosage and Administration	01/2025
4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	11/2025
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7 Warnings and Precautions, 7.1.4 Geriatrics	01/2025

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Part 1: Healthcare Professional Information

1 Indications

RYBREVANT (amivantamab for injection) is indicated:

- in combination with carboplatin and pemetrexed for the treatment of patients with locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) with epidermal-growth factor receptor (EGFR) Exon 19 deletions or Exon 21 L858R substitution mutations, whose disease has progressed on or after treatment with osimertinib.

A validated test is required to identify EGFR Exon 19 deletion or Exon 21 L858R substitution mutation-positive status prior to treatment (see 4.1 Dosing Considerations).

- in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with locally advanced (not amenable to curative therapy) or metastatic NSCLC with activating EGFR Exon 20 insertion mutations.

A validated test is required to identify EGFR Exon 20 insertion mutation-positive status prior to treatment (see 4.1 Dosing Considerations).

- as monotherapy for the treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy.

Clinical effectiveness of RYBREVANT monotherapy is based on objective response rate (ORR) and duration of response (DOR) from a single-arm trial in patients with activating epidermal-growth factor receptor (EGFR) Exon 20 insertion mutations.

A validated test is required to identify EGFR Exon 20 insertion mutation-positive status prior to treatment (see 4.1 Dosing Considerations).

1.1 Pediatrics:

- Based on the data submitted and reviewed by Health Canada, the safety and efficacy of RYBREVANT in pediatric patients (<18 years of age) has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics:

- No clinically relevant differences in effectiveness were observed between elderly patients (≥65 years of age) and younger patients. Evidence from the clinical studies suggests that the use in the geriatric population is associated with differences in safety (see 7.1.4 Geriatrics).

2 Contraindications

RYBREVANT is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition, and Packaging.

4 Dosage and Administration

4.1 Dosing Considerations

- RYBREVANT should be administered by a healthcare professional with appropriate medical support to manage infusion related reactions (IRRs) if they occur (see 7 Warnings and Precautions).
- When considering the use of RYBREVANT, before treatment initiation the presence of an EGFR Exon 19 deletion, Exon 21 L858R substitution, or Exon 20 insertion mutation is required to be determined using a validated test (see 14 Clinical Trials).
- Administer pre-infusion medications (see 4.2 Recommended Dose and Dosage Adjustment, Table 4).
- Administer RYBREVANT via peripheral line for all Cycle 1 doses to reduce the risk of infusion related reactions (see 4.4 Administration).
- Administer diluted RYBREVANT intravenously according to the infusion rates in Table 1 and Table 3, with the initial dose as a split infusion in Week 1 on Day 1 and Day 2.

4.2 Recommended Dose and Dosage Adjustment

It is recommended that patients are treated with RYBREVANT until disease progression or unacceptable toxicity (see 4.4 Administration). Pre-medications should be administered before each RYBREVANT infusion as recommended (see Recommended Pre-infusion medications and Table 4).

RYBREVANT in combination with carboplatin and pemetrexed

The recommended dosage of RYBREVANT, when used in combination with carboplatin and pemetrexed is provided in Table 1 (see infusion rates in Table 7).

When used in combination with carboplatin and pemetrexed, RYBREVANT should be administered after carboplatin and pemetrexed in the following order: pemetrexed, carboplatin and then RYBREVANT (see Table 2).

Table 1: Recommended Dose and Dosing Schedule for RYBREVANT when in combination with carboplatin and pemetrexed

Body weight at Baseline[a]	Recommended Dose	Schedule	Number of 350 mg/7 mL RYBREVANT Vials/dose
Less than 80 kg	1400 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1 • Weeks 5 and 6 – no dose	4
	1750 mg	**Every 3 weeks starting at Week 7 onwards**	5
Greater than or equal to 80 kg	1750 mg	Weekly (total of 4 doses) for Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1 • Week 5 and 6 – no dose	5
	2100 mg	**Every 3 weeks starting at Week 7 onwards**	6

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

Table 2: Recommended order of administration and regimen for RYBREVANT in combination with carboplatin and pemetrexed

RYBREVANT in Combination with Carboplatin and Pemetrexed		
Administer the regimen in the following order: pemetrexed first, carboplatin second and RYBREVANT last.		
Drug	**Dose**	**Duration/Timing of Treatment**
Pemetrexed	Pemetrexed 500 mg/m^2 intravenously Refer to the pemetrexed Product Monograph for complete information.	Every 3 weeks, continue until disease progression or unacceptable toxicity.
Carboplatin	Carboplatin AUC 5 intravenously Refer to the carboplatin Product Monograph for complete information.	Every 3 weeks for up to 12 weeks.
RYBREVANT	RYBREVANT intravenously See Table 1.	Every 3 weeks, continue until disease progression or unacceptable toxicity.

RYBREVANT monotherapy

The recommended dosage of RYBREVANT monotherapy is provided in Table 3 (see infusion rates in Table 8).

Table 3: Recommended Dose and Dosing Schedule for RYBREVANT monotherapy

Body weight at Baseline[a]	Recommended Dose	Dosing Schedule	Number of 350 mg/7 mL RYBREVANT Vials/dose
Less than 80 kg	1050 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1	3
		Every 2 weeks starting at Week 5 onwards	
Greater than or equal to 80 kg	1400 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1	4
		Every 2 weeks starting at Week 5 onwards	

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

Recommended Pre-infusion medications

Two days before the first (initial) infusion only:

Oral dexamethasone or equivalent

Starting two days prior to the initial RYBREVANT infusion, patients should receive 8 mg dexamethasone orally, twice daily (total 16 mg per day). On the day of the initial infusion (Week 1, Day 1), patients should receive 8 mg dexamethasone orally, one hour prior to infusion in addition to intravenous dexamethasone to further reduce the risk of IRR.

Day of initial and subsequent Infusions:

Prior to the initial infusion of RYBREVANT (Week 1, Days 1 and 2), administration of antihistamines, antipyretics, and glucocorticoids is required to reduce the risk of IRRs as described in Table 4. For subsequent doses, administer both antihistamines and antipyretics prior to all infusions, and glucocorticoids as necessary. Administer antiemetics as needed. After prolonged dose interruptions of RYBREVANT, restart the premedications upon reinitiation of treatment: intravenous dexamethasone, diphenhydramine, and acetaminophen (see Table 4).

Table 4: 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[*]	Acetaminophen (650 to 1,000 mg)	IV	15 to 30 minutes
		Oral	30 to 60 minutes
Glucocorticoid[‡]	Dexamethasone (20 mg) or equivalent	IV	60 to 120 minutes

Medication	Dose	Route of Administration	Dosing Window Prior to RYBREVANT Administration
Glucocorticoid[+]	Dexamethasone (10 mg) or equivalent	IV	45 to 60 minutes

[*] Required at all doses.
[‡] Required at initial dose (Week 1, Day 1)
[+] Required at second dose (Week 1, Day 2); optional for subsequent doses

Dose Modifications

The recommended RYBREVANT dose reductions for adverse reactions (see Table 6) are outlined in Table 5.

Table 5 : RYBREVANT Dose Reductions for Adverse Reactions

Dose*	1st Dose Reduction	2nd Dose Reduction	3rd Dose Modification
1050 mg	700 mg	350 mg	Discontinue RYBREVANT
1400 mg	1050 mg	700 mg	
1750 mg	1400 mg	1050 mg	
2100 mg	1750 mg	1400 mg	

* Dose at which the adverse reaction occurred

Table 6: Dose Modifications for Adverse Reactions

Adverse Reaction	Severity	Dose Modification
Infusion Related Reactions (IRRs) (see 7 Warnings and Precautions)	Grade 1 to 3	• Interrupt RYBREVANT infusion at the first sign of IRRs. Monitor patients until symptoms resolve. • 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 7 and Table 8). • Pre-medications should be administered prior to the next dose (see Table 4).
	Recurrent Grade 3 or any Grade 4	Permanently discontinue RYBREVANT

Adverse Reaction	Severity	Dose Modification
Interstitial Lung Disease (ILD) / Pneumonitis (see 7 Warnings and Precautions)	Suspected ILD/ pneumonitis (any Grade)	Withhold RYBREVANT
	Confirmed ILD/ pneumonitis (any Grade)	Permanently discontinue RYBREVANT
Skin and Nail Reactions (see 7 Warnings and Precautions)	Grade 1	• Supportive care should be initiated. • Reassess after 2 weeks.
	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 RYBREVANT until the adverse reaction improves. Upon recovery to ≤ Grade 2, resume RYBREVANT at reduced dose (see Table 5). • If no improvement within 2 weeks, permanently discontinue treatment.
	Grade 4, and severe bullous, blistering, or exfoliating skin conditions, including toxic epidermal necrolysis (TEN)	Permanently discontinue RYBREVANT
Other Adverse Reactions (see 8 Adverse Reactions)	Grade 3	• Withhold RYBREVANT until adverse reaction improves to ≤ Grade 1 or baseline. • Resume at same dose if recovery occurs within 1 week. • Resume RYBREVANT at reduced dose (see Table 5) if recovery occurs after 1 week. • Permanently discontinue RYBREVANT if recovery does not occur within 4 weeks.
	Grade 4	• Withhold RYBREVANT until adverse reaction improves to ≤ Grade 1 or baseline. • Resume at reduced dose (see Table 5) if recovery occurs within 4 weeks.

Adverse Reaction	Severity	Dose Modification
		• Permanently discontinue RYBREVANT if recovery does not occur within 4 weeks. • Permanently discontinue RYBREVANT for recurrent Grade 4 reactions.

Recommended Dose Modifications for Adverse Reactions for RYBREVANT in Combination with Carboplatin and Pemetrexed

When administering RYBREVANT in combination with carboplatin and pemetrexed, follow the recommended dose modifications for adverse reactions for RYBREVANT as shown in Table 6. Refer to the Product Monographs for carboplatin and pemetrexed for their dosage modification recommendations.

Renal impairment

No formal studies of RYBREVANT in patients with renal impairment have been conducted. Based on population pharmacokinetic (PK) analyses, no dosage adjustment is necessary for patients with mild (60 ≤ creatinine clearance [CrCl] < 90 mL/min) or moderate (29 ≤ CrCl < 60 mL/min) renal impairment. No data are available in patients with severe renal impairment (15 ≤ CrCl < 29 mL/min) (see 10.3 Pharmacokinetics).

Hepatic impairment

No formal studies of RYBREVANT in patients with hepatic impairment have been conducted. Based on population PK analyses, no dosage adjustment is necessary for patients with mild hepatic impairment [(total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5 x ULN)]. No data are available in patients with moderate (total bilirubin 1.5 to 3 times ULN) or severe (total bilirubin >3 times ULN) hepatic impairment (see 10.3 Pharmacokinetics).

Pediatrics (<18 years)

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

Geriatrics (≥65 years)

No dose adjustment of RYBREVANT is required in patients aged 65 years or older. (see 7.1.4 Geriatrics and see 10.3 Pharmacokinetics).

4.3 Reconstitution

Parenteral Products: **Dilution**

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

- Determine the dose required and number of RYBREVANT vials needed based on patient's baseline weight (see 4.2 Recommended Dose and Dosage Adjustment). Each vial of RYBREVANT contains 350 mg of amivantamab.

- Check that the RYBREVANT solution is colorless to pale yellow. Do not use if discoloration or visible particles are present.
- Withdraw and then discard a volume of either 5% dextrose [glucose] solution USP or 0.9% sodium chloride solution USP 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).
- 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.
- Gently invert the bag to mix the solution. Do not shake.
- Visually inspect the diluted solution before administration. Do not use if discoloration or visible particles are observed.
- Diluted solutions should be administered within 10 hours (including infusion time of 2-5 hours, Table 7 and Table 8) at room temperature (15°C to 25°C) and in room light (see 11 Storage, Stability and Disposal).

4.4 Administration

- Due to the frequency of infusion related reactions (IRRs; see 7 Warnings and Precautions) at the first dose, RYBREVANT must be infused via a peripheral line for all Cycle 1 doses (Week 1 to Week 4) to minimize drug exposure in the event of an IRR. If peripheral access is limiting, earlier use of a central line in Cycle 1 starting after Cycle 1 Day 8 may be considered if deemed medically acceptable.
- RYBREVANT via a central line may be considered for subsequent weeks.
- For the first dose, RYBREVANT should be diluted as close to administration as possible to allow for maximal flexibility for infusion time and allow for IRR management.
- Prior to administration, prime the infusion set with the diluent (either 5% dextrose solution or 0.9% sodium chloride solution).
- 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), primed with diluent only. Administration sets must be made of either polyurethane (PU), polybutadiene (PBD), PVC, PP, or PE.
- Do not infuse RYBREVANT concomitantly in the same intravenous line with other agents.
- This medicinal product is for single use only. Any unused medicinal product should be disposed of in accordance with local requirements.

RYBREVANT in combination with carboplatin and pemetrexed

- Administer RYBREVANT, when used in combination with carboplatin and pemetrexed, intravenously at the recommended dose as per Table 1 and according to the infusion rates in Table 7.

- When used in combination with carboplatin and pemetrexed, RYBREVANT is administered weekly for the first four weeks. Patients do not receive RYBREVANT treatment in Week 5 or 6. RYBREVANT is administered at Week 7 and every 3 weeks thereafter.
- Administer treatment in the following order: pemetrexed infusion first, carboplatin infusion second, and the RYBREVANT infusion last according to Table 2.

Table 7: Infusion Rates for RYBREVANT when in combination with carboplatin and pemetrexed

Body Weight Less than 80 kg			
Week	**Dose (per 250 mL bag)**	**Initial Infusion Rate**	**Subsequent Infusion Rate†**
Week 1 (split dose infusion)			
Week 1 Cycle 1 *Day 1*	350 mg	50 mL/hr	75 mL/hr
Week 1 Cycle 1 *Day 2*	1050 mg	33 mL/hr	50 mL/hr
Week 2 Cycle 1 *Day 8*	1400 mg	65 mL/hr	
Week 3 Cycle 1 *Day 15*	1400 mg	85 mL/hr	
Week 4 Cycle 2 *Day 1*	1400 mg	125 mL/hr	
Week 5 and 6	No dose		
Week 7 Cycle 3 *Day 1* **and Subsequent weeks***	1750 mg	125 mL/hr	
Body Weight Greater Than or Equal to 80 kg			
Week	**Dose (per 250 mL bag)**	**Initial Infusion Rate**	**Subsequent Infusion Rate†**
Week 1 (split dose infusion)			
Week 1 Cycle 1 *Day 1*	350 mg	50 mL/hr	75 mL/hr
Week 1 Cycle 1 *Day 2*	1400 mg	25 mL/hr	50 mL/hr
Week 2 Cycle 1 *Day 8*	1750 mg	65 mL/hr	
Week 3 Cycle 1 *Day 15*	1750 mg	85 mL/hr	
Week 4 Cycle 2 *Day 1*	1750 mg	125 mL/hr	
Week 5 and 6	No dose		
Week 7 Cycle 3 *Day 1* **and Subsequent weeks***	2100 mg	125 mL/hr	

* Starting at Week 7 (start of Cycle 3), patients are dosed every 3 weeks.
† Increase the initial infusion rate to the subsequent infusion rate after 2 hours in the absence of infusion related reactions.

RYBREVANT monotherapy

- Administer RYBREVANT as a monotherapy at the recommended dose as per Table 3 and according to the infusion rates in Table 8.
- As a monotherapy, RYBREVANT is administered weekly for the first four weeks. RYBREVANT is then administered at Week 5 and every 2 weeks thereafter.

Table 8: Infusion Rates for RYBREVANT monotherapy

Body Weight Less Than 80 kg			
Week	**Dose (per 250 mL bag)**	**Initial Infusion Rate**	**Subsequent Infusion Rate†**
Week 1 (split dose infusion)			
Week 1 Cycle 1 *Day 1*	350 mg	50 mL/hr	75 mL/hr
Week 1 Cycle 1 *Day 2*	700 mg	50 mL/hr	75 mL/hr
Week 2 Cycle 1 *Day 8*	1050 mg	85 mL/hr	
Week 3 Cycle 1 *Day 15*	1050 mg	125 mL/hr	
Week 4 Cycle 1 *Day 22*	1050 mg	125 mL/hr	
Week 5 Cycle 2 *Day 1* **and subsequent weeks/cycles***	1050 mg	125 mL/hr	
Body Weight Greater Than or Equal to 80 kg			
Week	**Dose (per 250 mL bag)**	**Initial Infusion Rate**	**Subsequent Infusion Rate†**
Week 1 (split dose infusion)			
Week 1 *Day 1* Cycle 1 *Day 1*	350 mg	50 mL/hr	75 mL/hr
Week 1 *Day 2* Cycle 1 *Day 2*	1050 mg	35 mL/hr	50 mL/hr
Week 2 Cycle 1 *Day 8*	1400 mg	65 mL/hr	
Week 3 Cycle 1 *Day 15*	1400 mg	85 mL/hr	
Week 4 Cycle 1 *Day 22*	1400 mg	125 mL/hr	
Week 5 Cycle 2 *Day 1* **and subsequent weeks/cycles***	1400 mg	125 mL/hr	

* Starting at week 5 (start of Cycle 2), patients are dosed every 2 weeks.
† Increase the initial infusion rate to the subsequent infusion rate after 2 hours in the absence of infusion related reactions.

4.5 Missed Dose

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.

5 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, monitor patient for any signs or symptom of adverse reactions and undertake general supportive measures until clinical toxicity has diminished or resolved.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition, and Packaging

To help ensure the traceability of biologic products, healthcare professionals should record both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 9: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous (IV) infusion	Liquid concentrate for IV infusion 350mg/7mL	EDTA disodium salt dihydrate, L-Histidine, L-Histidine hydrochloride monohydrate, L--Methionine, Polysorbate 80, Sucrose, Water for Injection

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

Each single-use vial contains 350 mg of amivantamab per 7 mL (or 50 mg of amivantamab per mL). Each vial is individually packaged in a carton.

7 Warnings and Precautions

General

The safety data described in the 7 Warnings and Precautions section reflects the safety profile of 281 patients with locally advanced or metastatic non small cell lung cancer (NSCLC) including 130 patients who received RYBREVANT in combination with carboplatin and pemetrexed in the MARIPOSA-2 study and 151 patients who received RYBREVANT in

combination with carboplatin and pemetrexed in the PAPILLON study.

The safety data described in the 7 Warnings and Precautions section also reflects exposure of 302 patients, with locally advanced or metastatic NSCLC to RYBREVANT monotherapy in the CHRYSALIS study. This includes 129 patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy. Patients were treated at a dose of 1050 mg (for patients <80 kg) or 1400 mg (for patients ≥80 kg) once weekly for 4 weeks, then every 2 weeks starting at Week 5.

Carcinogenesis and Genotoxicity

No animal studies have been performed to evaluate the carcinogenic or mutagenic potential of amivantamab (see 16 Non-Clinical Toxicology).

Driving and Operating Machinery

No studies on the effects on the ability to drive and use machines have been performed. Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

If patients experience treatment-related symptoms affecting their ability to concentrate and react, it is recommended that they do not drive or use machines until the effect subsides.

Immune

Infusion related reactions may occur in patients treated with RYBREVANT. The most frequent signs and symptoms include chills, nausea, dyspnea, flushing, chest discomfort, hypotension, and vomiting.

RYBREVANT in combination with carboplatin and pemetrexed

Infusion related reactions (IRRs) occurred in 49.5% of patients treated with RYBREVANT. Among patients receiving treatment on Week 1 Day 1, 45.7% experienced an IRR, while the incidence of IRR was 1.5% with the Day 2 infusion, 2.1% with the Week 2 infusion, and cumulatively 8.2% with subsequent infusions. Of the cases that reported IRRs, 93.5.% were Grade 1-2, 6.5% were Grade 3, and 0% were Grade 4. The median time to onset was 1.0 hours (range 0.0 to 7 hours) after start of infusion. The incidence of dose reduction due to IRR was 0.4%, and 2.8% of patients permanently discontinued RYBREVANT due to IRR.

RYBREVANT as monotherapy

Infusion related reactions (IRRs) occurred in 66% of patients treated with RYBREVANT. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the cases that reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62.3% and 1.3% of patients permanently discontinued RYBREVANT due to IRR.

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, Day 1, and Day 2. Administer RYBREVANT via a peripheral line for all Cycle 1 doses (Week 1 to Week 4) (see 4 Dosage and Administration).

To reduce the risk of infusion related reactions, administer pre-infusion oral dexamethasone starting 2 days prior to the initial infusion followed by the recommended pre-infusion medications to be administered on the day of initial infusion (Table 4) (see 4 Dosage and Administration, Pre-infusion medications). The addition of oral dexamethasone demonstrated a reduction in incidence and severity of IRRs on the day of the initial infusion.

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 4 Dosage and Administration).

Ophthalmologic

Eye disorders may occur in patients treated with RYBREVANT.

RYBREVANT in combination with carboplatin and pemetrexed

Eye disorders, including keratitis (0.4%), occurred in 10.7% of patients treated with RYBREVANT. Other reported adverse reactions included dry eye, blurred vision, eye pruritus, visual impairment, ocular hyperemia, aberrant eyelash growth, conjunctival hyperemia, blepharitis, and uveitis. All events were Grade 1-2.

RYBREVANT as monotherapy

Eye disorders, including keratitis (0.7%), occurred in 13.2% patients treated with RYBREVANT. Other reported adverse reactions included dry eye, blurred vision, eye pruritus, lacrimation increased, visual impairment, ocular hyperemia, eyelid ptosis, aberrant eyelash growth, 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. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity (see 4 Dosage and Administration).

Reproductive Health: Female and Male Potential

Due to the risk that RYBREVANT can cause fetal 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 (see 7.1.1 Pregnancy). 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.

- **Fertility**

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

females (see 7.1.1 Pregnancy).

- **Teratogenic Risk**

  Administration of other EGFR and MET inhibitor molecules to pregnant animals has resulted in an increased incidence of impairment of embryo-fetal development, embryolethality, and abortion. Therefore, based on its mechanism of action and findings in animal models, RYBREVANT could cause fetal harm when administered to a pregnant woman (also see 7.1.1 Pregnancy).

Respiratory

Interstitial lung disease (ILD/pneumonitis may occur in patients treated with RYBREVANT.

RYBREVANT in combination with carboplatin and pemetrexed

Interstitial lung disease (ILD) or ILD-like adverse reactions (e.g. pneumonitis) occurred in 2.1% of patients treated with RYBREVANT, with 1.8% of patients experiencing Grade 3 ILD. Six patients (2.1%) discontinued RYBREVANT due to ILD/pneumonitis.

RYBREVANT as monotherapy

ILD or ILD-like adverse reactions (e.g. pneumonitis) occurred in 3.3% of patients treated with RYBREVANT, with 0.7% of patients experiencing Grade 3 ILD. Three patients (1%) discontinued RYBREVANT due to ILD/pneumonitis.

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 studies.

Monitor patients for symptoms indicative of ILD/pneumonitis (e.g., dyspnea, 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 4 Dosage and Administration).

Skin

Skin and nail reactions may occur in patients treated with RYBREVANT.

RYBREVANT in combination with carboplatin and pemetrexed

Rash (including dermatitis acneiform) (81.9%), pruritus (10.7%) and dry skin (15.7%) occurred in patients treated with RYBREVANT. Most cases were Grade 1 or 2, with Grade 3 events occurring in 15.3% of patients. Rash leading to dose reduction occurred in 13.5% of patients, and RYBREVANT discontinuation due to rash occurred in 2.5% of patients. Rash usually developed within the first 4 weeks of therapy, with a median time to onset of 14 days (range: 1 to 311 days). Nail toxicity occurred in patients treated with RYBREVANT. All events were Grade 1 or 2, with Grade 3-4 nail toxicity occurring in 0% of patients.

RYBREVANT as monotherapy

Rash (including dermatitis acneiform) (73.5%), pruritis (17.9%) and dry skin (10.9%) occurred in patients treated with RYBREVANT. Most cases were Grade 1 or 2, with Grade 3 events occurring in 3.6% of patients. Rash leading to dose reduction occurred in 5% of patients and RYBREVANT discontinuation due to rash occurred in 0.7% of patients. Rash usually developed within the first 4 weeks of therapy, with a median time to onset of 14 days (range: 1 to 276 days). Paronychia occurred in patients treated with RYBREVANT. Most events were Grade 1 or 2, with Grade 3 paronychia occurring in 1.4% of patients.

Toxic epidermal necrolysis (TEN) occurred in one patient (0.2%) treated with RYBREVANT. Permanently discontinue RYBREVANT if TEN is confirmed.

A prophylactic approach to rash prevention should be considered. Instruct patients to limit sun exposure during and for 2 months after RYBREVANT therapy. Protective clothing and use of sunscreen are 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. For Grade 4 skin reactions, permanently discontinue RYBREVANT. 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 4 Dosage and Administration).

7.1 Special Populations

7.1.1 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-fetal development, embryolethality, and abortion. Therefore, based on its mechanism of action and findings in animal models, RYBREVANT could cause fetal harm when administered to a pregnant woman.

RYBREVANT should not be used during pregnancy unless the benefit of treatment to the woman is considered to outweigh potential risks to the fetus. If the patient becomes pregnant while taking this drug, the patient should be informed of the potential risk to the fetus.

7.1.2 Breast-feeding

No studies have been conducted to determine if RYBREVANT is excreted in human or animal milk or affects milk production. RYBREVANT is a fully human, Immunoglobulin G1 (IgG1) based bispecific antibody. In general, human IgGs are known to be excreted in breast milk during the first few days after birth, which decreases to lower concentrations soon afterwards. 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.

7.1.3 Pediatrics

The efficacy and safety of RYBREVANT in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Of the 281 patients treated with RYBREVANT in PAPILLON and MARIPOSA-2, 38% were 65 years of age or older, and 9% were 75 years of age or older. No clinically relevant differences in effectiveness were observed based on age. Adverse events that led to discontinuation of any study agent were reported for 13.8% of patients under 65 years old and 33.6% of patients aged 65 years or older.

Of the 302 patients treated with RYBREVANT in CHRYSALIS (EDI1001), 39.4% were 65 years of age or older, and 11.3% were 75 years of age or older. No clinically relevant differences in effectiveness were observed based on age. There was a higher incidence of serious adverse events observed in patients aged 65 years or older (39.5%) as compared to younger patients (25.1%). There was also a higher incidence of adverse events leading to dose interruptions observed in patients aged 65 years or older (44.5%) as compared to younger patients (28.4%).

8 Adverse Reactions

8.1 Adverse Reaction Overview

The following adverse reactions observed with RYBREVANT when used in combination with carboplatin and pemetrexed or when RYBREVANT is used alone as a monotherapy are discussed in the WARNINGS AND PRECAUTIONS section (7 Warnings and Precautions):

- Infusion Related Reactions (see 7 Warnings and Precautions, Immune)
- Eye Disorders (see 7 Warnings and Precautions, Ophthalmologic)
- Interstitial Lung Disease (ILD)/Pneumonitis (see 7 Warnings and Precautions, Respiratory)
- Skin and Nail Reactions (see 7 Warnings and Precautions, Skin)

RYBREVANT in Combination with Carboplatin and Pemetrexed

The pooled safety population described in the 7 Warnings and Precautions also reflect exposure to RYBREVANT in combination with carboplatin and pemetrexed in 281 patients in two studies:

- MARIPOSA-2 (NSC3002) in 130 patients
- PAPILLON (NSC3001) in 151 patients

Among 281 patients who received RYBREVANT in combination with carboplatin and pemetrexed, 65% were exposed for 6 months or longer and 24% were exposed for greater

than one year.

Two hundred and eighty-one patients were exposed to RYBREVANT with carboplatin and pemetrexed in PAPILLON (N=151) and MARIPOSA-2 (N=130) for a median duration of 7.75 (range 0 to 26.9) months and to carboplatin and pemetrexed (N=398) for a median duration of 4.86 (range 0 to 25.3) months.

The most common adverse reactions ≥20% were rash, neutropenia, infusion related reactions, paronychia, fatigue, anemia, nausea, thrombocytopenia, stomatitis, constipation, edema, decreased appetite, leukopenia, hypoalbuminemia, alanine aminotransferase increased, aspartate aminotransferase increased, and vomiting.

The most common grade 3 to grade 4 laboratory abnormalities ≥2% were decreased neutrophil count, decreased white blood cell count, decreased lymphocyte count, decreased platelet count, decreased hemoglobin, decreased potassium, decreased sodium, decreased albumin, increased alanine aminotransferase, and increased gamma glutamyl transferase.

RYBREVANT as a Monotherapy

Previously Treated NSCLC with EGFR Exon 20 Insertion Mutations (CHRYSALIS Study)

The safety of RYBREVANT described in the 8 Adverse Reactions section reflects the exposure of 129 patients enrolled in the CHRYSALIS study. The most common adverse reactions ≥ 20% were dermatitis acneiform, rash, infusion related reactions (IRRs), nausea, paronychia, fatigue, hypoalbuminemia, constipation, stomatitis, peripheral edema, and alanine aminotransferase increased. The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were decreased albumin, decreased phosphates, decreased potassium, increased alkaline phosphatase, increased glucose, increased gamma-glutamyltransferase, decreased sodium, increased alanine aminotransferase, decreases in lymphocytes, neutrophils, hemoglobin, and white blood cells.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Previously Treated NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations

The safety of RYBREVANT in combination with carboplatin and pemetrexed was evaluated in MARIPOSA-2 (NSC3002), which included patients with locally advanced or metastatic NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations whose disease has progressed on or after treatment with osimertinib. (see 14 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 3 weeks with a dose of 1750 mg (for patients

< 80 kg) or 2100 mg (for patients ≥ 80 kg) starting at Week 7 until disease progression or unacceptable toxicity.

Patients were exposed to RYBREVANT with carboplatin and pemetrexed (N=130) for a median treatment duration of 6.3 (range: 0 to 14.7) months and to carboplatin and pemetrexed (N=243) for a median treatment duration of 3.7 (range: 0 to 15.9) months.

The most common TEAE (≥ 20%) in patients who received RYBREVANT in combination with carboplatin and pemetrexed were infusion related reactions, neutropenia, nausea, rash, thrombocytopenia, anemia, constipation, paronychia, edema peripheral, stomatitis, decreased appetite, leukopenia, fatigue, asthenia, vomiting, hypoalbuminemia, COVID-19, alanine aminotransferase increased, and dermatitis acneiform. The most common TEAE (≥ 20%) in patients who received carboplatin and pemetrexed were neutropenia, anemia, nausea, thrombocytopenia, constipation, leukopenia, alanine aminotransferase increased, aspartate aminotransferase increased, and decreased appetite.

Dose interruptions of RYBREVANT due to an adverse reaction occurred in 60% of patients. Infusion related reactions (IRRs) requiring infusion interruptions occurred in 52% of patients. Adverse reactions requiring dose interruption in ≥5% of patients included neutropenia, thrombocytopenia, COVID-19, leukopenia, and rash. Dose reductions of RYBREVANT due to an adverse reaction occurred in 17% of patients. The most commonly reported adverse reactions requiring dose reductions in ≥ 2% of patients included neutropenia and rash.

Fifteen percent of patients permanently discontinued RYBREVANT due to adverse reactions. The most frequent adverse reactions leading to treatment discontinuation in ≥ 1% of patients were infusion related reactions.

The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were decreased albumin, increased alanine aminotransferase, increased gamma-glutamyl transferase, decreased sodium, decreased potassium, decreases in white blood cells, hemoglobin, neutrophils, platelets, and lymphocytes.

Serious adverse events occurred in 32.3% of patients who received RYBREVANT in combination with carboplatin and pemetrexed, and in 20.2% of patients treated with chemotherapy alone. In MARIPOSA-2 ACP arm, Grade≥ 3 TEAEs were reported for 79.0% of Asians and in 64.1% of non-Asians. SAEs were reported for 40.3% of Asians and in 23.4% of non-Asians.

Serious adverse events in ≥ 2% of patients who received RYBREVANT in combination with carboplatin and pemetrexed included thrombocytopenia, dyspnea, sepsis, and pulmonary embolism. Serious adverse events in ≥ 2% who received chemotherapy alone included neutropenia, thrombocytopenia, febrile neutropenia, and pneumonia. Fatal adverse reactions, irrespective of relatedness to treatment occurred in 3 patients (2.3%) who received RYBREVANT in combination with carboplatin and pemetrexed. Fatal adverse reactions, irrespective of relatedness to treatment occurred in 3 patients (1.2%) who received chemotherapy alone. The fatal adverse events that occurred in patients treated with RYBREVANT in combination with carboplatin and pemetrexed included dyspnea, sepsis, and

ventricular fibrillation. The fatal adverse reactions that occurred in patients treated with chemotherapy alone included dyspnea, pneumonia, and respiratory failure.

Table 10 summarizes TEAEs reported in ≥5% of patients in MARIPOSA-2.

Table 10: Treatment-Emergent Adverse Events (≥5%) in Previously Treated Patients with NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations Treated with RYBREVANT in Combination with Carboplatin and Pemetrexed in MARIPOSA-2

System Organ Class Adverse Reaction	**RYBREVANT + Carboplatin + Pemetrexed (N=130)**		**Carboplatin + Pemetrexed (N=243)**	
	All Grades (%)	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Blood and lymphatic disorders				
Neutropenia	57	45	42	21
Thrombocytopenia	44	15	30	9.1
Anemia	39	12	40	10
Leukopenia	29	20	28	10
Eye disorders				
Eye disorders[a]	13	0	5	0
Gastrointestinal disorders				
Nausea	45	0.8	37	0.8
Constipation	39	0.8	30	0
Stomatitis[b]	35	2.3	11	0
Vomiting	25	0.8	17	0.4
Diarrhea	14	0.8	6.6	0.4
Abdominal pain[c]	9.2	0	6.6	0
Hemorrhoids	5.4	0	0.4	0
General disorders and administration site conditions				
Fatigue[d]	51	3.8	35	3.7
Edema[e]	36	1.5	11	0.4
Pyrexia	12	0	10	0
Injury, poisoning and procedural complications				
Infusion related reaction	59	5.4	0.4	0
Infections and infestations				
Paronychia	37	2.3	0.4	0
COVID-19	21	1.5	10	0
Conjunctivitis	7.7	0	2.1	0
Investigations				
Alanine aminotransferase increased	20	5.4	28	4.1
Aspartate aminotransferase increased	15	0.8	24	0
Weight decreased	11	0	7.0	0.4
Blood alkaline phosphatase increased	6.9	0	5.3	0

System Organ Class Adverse Reaction	**RYBREVANT + Carboplatin + Pemetrexed (N=130)**		**Carboplatin + Pemetrexed (N=243)**	
Gamma-glutamyl transferase increased	5.4	2.3	10	0.4
Metabolism and nutrition disorders				
Decreased appetite	31	0	21	1.2
Hypoalbuminemia	22	2.3	8.6	0.4
Hypokalemia	19	4.6	6.2	2.5
Hyperglycemia	12	0.8	4.1	0
Hypocalcaemia	12	0.8	3.7	0
Hypomagnesemia	10	0.8	3.7	0
Hyponatremia	10	3.8	6.6	0.8
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[f]	22	3.1	14	0.8
Nervous system disorders				
Dizziness[g]	9.2	0	6.6	0
Headache	8.5	0	12	0.4
Psychiatric disorders				
Insomnia	7.7	0	2.9	0
Respiratory, thoracic and mediastinal disorders				
Cough	11	0	12	0.4
Dyspnea	11	1.5	7.4	1.2
Epistaxis	8.5	0	2.9	0
Skin and subcutaneous tissue disorders				
Rash[h]	72	11	12	0
Nail toxicity[i]	8.5	0	0	0
Pruritus	15	0	7.0	0
Dry skin[j]	15	0	2.5	0
Alopecia	6.2	0	3.3	0
Vascular disorders				
Venous thromboembolism[k]	6.9	2.3	3.3	2.5

System Organ Class Adverse Reaction	**RYBREVANT + Carboplatin + Pemetrexed (N=130)**	**Carboplatin + Pemetrexed (N=243)**
Adverse events are coded using MedDRA Version 25.0 [a] includes Blepharitis, Conjunctival hyperemia, Dry eye, Eye pruritus, Keratitis, Noninfective conjunctivitis, Ocular hyperaemia, Trichomegaly, Uveitis, Vision blurred, Visual acuity reduced, Visual impairment [b] includes Angular cheilitis, Aphthous ulcer, Cheilitis, Glossitis, Lip ulceration, Mouth ulceration, Mucosal inflammation, Stomatitis [c] includes Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper [d] includes Asthenia, Fatigue, Malaise [e] includes Eye edema, Eyelid edema, Face edema, Generalised edema, Localised edema, Edema, Edema peripheral, Periorbital edema, Peripheral swelling, Swelling face [f] includes Arthralgia, Back pain, Pain in extremity [g] includes Dizziness, Vertigo [h] includes Acne, Dermatitis, Dermatitis acneiform, Erythema, Folliculitis, Impetigo, Palmar-plantar erythrodysaesthesia syndrome, Perioral dermatitis, Pustule, Rash, Rash erythematous, Rash follicular, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash pustular, Skin exfoliation, Skin lesion [i] includes Ingrowing nail, Nail bed disorder, Nail bed inflammation, Nail disorder, Nail dystrophy, Nail infection, Onychoclasis, Onycholysis, [j] includes Dry skin, Eczema, Skin fissures, Xeroderma, Xerosis [k] includes Deep vein thrombosis and Pulmonary embolism		

First-line Treatment of Non-Small Cell Lung Cancer (NSCLC) with EGFR Exon 20 Insertion Mutations

The safety of RYBREVANT in combination with carboplatin and pemetrexed was evaluated in the PAPILLON study, a randomized, open-label trial in patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations (see 14.1 Clinical Trials by Indication). In the PAPILLON study, 151 patients were treated with RYBREVANT at the recommended dosage and 155 patients were treated with carboplatin and pemetrexed (chemotherapy alone). Among patients who received RYBREVANT in combination with carboplatin and pemetrexed, the median exposure was 9.7 months (range: 0.1 to 26.9 months). The median exposure for patients who received chemotherapy alone was 6.7 months (range: 0.0 to 25.3 months). The median age was 62 years (range: 27 to 92 years); 57.8% were female; 61.4% were Asian, 36.0% were White and 84.4% had baseline body weight <80 kg.

The most common TEAE (≥ 20%) in patients who received RYBREVANT in combination with carboplatin and pemetrexed were rash, neutropenia, paronychia, anaemia, stomatitis, infusion related reactions, hypoalbuminaemia, edema, constipation, leukopenia, nausea, thrombocytopenia, decreased appetite, fatigue, ALT increased, AST increased, COVID-19, hypokalaemia, vomiting, and diarrhea. The most common TEAE (≥ 20%) in patients who received chemotherapy alone were anaemia, neutropenia, nausea, fatigue, ALT increased, AST increased, leukopenia, constipation, thrombocytopenia, and decreased appetite.

Serious adverse events occurred in 37.1% of patients who received RYBREVANT in combination with carboplatin and pemetrexed, and in 31.0% of patients treated with chemotherapy alone. Serious adverse events in ≥ 2% of patients who received RYBREVANT in combination with carboplatin and pemetrexed included pneumonia, COVID-19, pulmonary embolism, thrombocytopenia, rash, interstitial lung disease/pneumonitis, vomiting, and hypokalemia. Serious adverse events in ≥ 2% of patients who received chemotherapy alone included pneumonia, pulmonary embolism, dyspnoea, pleural effusion, thrombocytopenia, and anaemia. Fatal adverse events, irrespective of relatedness to treatment, occurred in 7 patients (4.6%) who received RYBREVANT in combination with carboplatin and pemetrexed and 4 (2.6%) patients who received chemotherapy alone. The fatal adverse events that occurred in patients who received RYBREVANT in combination with carboplatin and pemetrexed included pneumonia, cardiovascular accident, cardio-respiratory arrest, COVID-19, sepsis and death. The fatal adverse events that occurred in patients treated with chemotherapy alone included sepsis, acute myocardial infarction, dyspnoea and death.

Permanent discontinuation of RYBREVANT due to an adverse event occurred in 11.3% of patients. Adverse events resulting in permanent discontinuation of RYBREVANT in ≥ 1% of patients were rash and ILD/pneumonitis.

Dose interruptions of RYBREVANT due to an adverse event occurred in 64.2% of patients. Infusion related reactions (IRRs) requiring infusion interruptions occurred in 37.7% of patients. Adverse events requiring dose interruption in ≥ 5% of patients included rash, neutropenia, paronychia, COVID-19, thrombocytopenia, and hypokalemia.

Dose reductions of RYBREVANT due to an adverse event occurred in 35.8% of patients. Adverse events requiring dose reductions in ≥ 5% of patients included rash and paronychia.

The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) observed in patients who received RYBREVANT in combination with carboplatin and pemetrexed were decreased albumin, increased alanine aminotransferase, increased gamma-glutamyltransferase, decreased sodium, decreased potassium, decreased magnesium and decreases in white blood cells, hemoglobin, neutrophils, platelets, and lymphocytes. The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) observed in patients who received chemotherapy alone were decreased sodium, increased gamma-glutamyltransferase and decreases in white blood cells, hemoglobin, neutrophils, platelets, and lymphocytes.

Table 11 summarizes the TEAEs reported in ≥5% of patients in the PAPILLON study.

Table 11: Treatment-emergent Adverse Events (≥5%) in Patients with NSCLC with Exon 20 Insertion Mutations Treated with RYBREVANT in Combination with Carboplatin and Pemetrexed in PAPILLON

System Organ Class Adverse Reaction	**RYBREVANT + Carboplatin + Pemetrexed (N=151)**		**Carboplatin + Pemetrexed (N=155)**	
	All Grades (%)	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**

System Organ Class Adverse Reaction	RYBREVANT + Carboplatin + Pemetrexed (N=151)		Carboplatin + Pemetrexed (N=155)	
Blood and Lymphatic system disorders				
Neutropenia	58.9	33.1	45.2	22.6
Anaemia	50.3	10.6	54.8	12.3
Leukopenia	37.7	11.3	32.3	3.2
Thrombocytopenia	36.4	9.9	29.7	10.3
Eye Disorders				
Eye disorders[a]	8.6	0	8.4	0
Gastrointestinal disorders				
Stomatitis[b]	43.0	4.0	11.0	0
Constipation	39.7	0	30.3	0.6
Nausea	36.4	0.7	41.9	0
Vomiting	21.2	3.3	18.7	0.6
Diarrhea	20.5	3.3	12.9	1.3
Hemorrhoids	11.9	1.3	1.3	0
Abdominal pain[c]	10.6	0.7	8.4	0
Gingival bleeding	5.3	0	1.3	0
Abdominal distension	4.6	0	6.5	0
General disorders and administration site conditions				
Edema[d]	40.4	1.3	18.7	0
Fatigue[e]	33.8	6.0	37.4	3.9
Pyrexia	15.9	0	5.8	0
Malaise	10.6	0	7.7	0
Hepatobiliary disorders				
Hyperbilirubinaemia	9.9	0.7	3.9	0
Infections and infestations				
Paronychia	56.3	6.6	0	0
COVID-19	23.8	1.3	13.5	0.6
Pneumonia	11.3	4.0	6.5	1.9
Conjunctivitis	6.0	0	4.5	0
Injury, poisoning and procedural complications				
Infusion related reaction	41.7	1.3	1.3	0
Investigations				
Alanine aminotransferase increased	33.1	4.0	36.1	1.3
Aspartate aminotransferase increased	31.1	0.7	32.9	0.6
Gamma-glutamyltransferase increased	13.9	2.6	16.8	3.9
Weight decreased	13.9	0.7	8.4	0
Blood alkaline phosphatase increased	12.6	0.7	7.7	0
Blood lactate dehydrogenase increased	8.6	0	5.2	0
Blood creatinine increased	7.3	1.3	9.7	0
Metabolism and nutrition disorders				
Hypoalbuminaemia	41.1	4.0	9.7	0
Decreased appetite	35.8	2.6	27.7	1.3

System Organ Class Adverse Reaction	RYBREVANT + Carboplatin + Pemetrexed (N=151)		Carboplatin + Pemetrexed (N=155)	
Hypokalaemia	21.2	8.6	8.4	1.3
Hypomagnesaemia	14.6	2.0	9.7	0.6
Hypocalcaemia	12.6	1.3	1.9	0
Hyponatraemia	12.6	2.0	7.7	0.6
Hypophosphataemia	6.6	0	1.3	0
Hypoproteinaemia	6.6	0	1.9	0
Hyperglycaemia	5.3	0	7.1	0.6
Musculoskeletal and connective tissue disorders				
Myalgia	5.3	1.3	3.2	0.6
Nervous system disorders				
Dizziness[f]	9.9	0	11.6	0
Dysgeusia	6.0	0	6.5	0
Respiratory, thoracic and mediastinal disorders				
Cough	13.9	0	15.5	0
Dyspnoea	10.6	1.3	14.8	2.6
Pulmonary embolism	7.9	3.3	4.5	3.9
Productive cough	6.0	0	1.9	0
Psychiatric disorders				
Insomnia	10.6	0	12.9	0
Skin and subcutaneous tissue disorders				
Rash[g]	90.1	19.2	18.7	0
Dry skin[h]	16.6	0	5.8	0
Alopecia	8.6	0	5.2	0
Nail toxicity[i]	7.9	0	3.2	0
Skin ulcer	6.6	1.3	0.6	0
Pruritus	6.6	0	7.7	0
Vascular disorders				
Deep vein thrombosis	6.6	0	1.9	0

System Organ Class Adverse Reaction	RYBREVANT + Carboplatin + Pemetrexed (N=151)	Carboplatin + Pemetrexed (N=155)
Adverse events are coded using MedDRA Version 25.0 [a] includes Blepharitis, Conjunctival hyperaemia, Dry eye, Eye pruritus, Keratitis, Vision blurred, Visual acuity reduced, Visual impairment [b] includes Angular cheilitis, Aphthous ulcer, Cheilitis, Lip ulceration, Mouth ulceration, Mucosal inflammation, Stomatitis [c] includes Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Gastrointestinal pain [d] includes Eye edema, Eyelid edema, Face edema, Generalised edema, Localised edema, Edema, Edema peripheral, Periorbital edema, Peripheral swelling, Swelling face [e] includes Asthenia, Fatigue [f] includes Dizziness, Vertigo [g] includes Acne, Dermatitis, Dermatitis acneiform, Erythema, Folliculitis, Palmar-plantar erythrodysaesthesia syndrome, Pustule, Rash, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash pustular, Skin lesion [h] includes Dry skin, Eczema, Skin fissures, Xeroderma, Xerosis [i] includes Ingrowing nail, Nail bed inflammation, Nail disorder, Nail dystrophy, Nail infection, Onychoclasis, Onycholysis		

Previously Treated NSCLC with EGFR Exon 20 Insertion Mutations

The safety of RYBREVANT monotherapy in patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy was evaluated in 129 patients enrolled in CHRYSALIS. 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: 0.03 to 23.9 months), with 44.2% of patients for at least 6 months. The median age was 62 years (range: 36 to 84 years) with 41.1% of patients 65 years of age or older, and 8.5% of patients 75 years of age or older; 61.2% were female; 55.0% were Asian, 2.3% were Black, and 34.9% were White. Eighty-two percent of patients (n=106) had baseline body weight <80 kg and 18% (n=23) had baseline body weight ≥80 kg.

The most common adverse reactions ≥ 20% were dermatitis acneiform, rash, infusion related reactions (IRRs), nausea, paronychia, fatigue, hypoalbuminemia, constipation, stomatitis, and peripheral edema, and alanine aminotransferase increased. Serious adverse reactions occurred in 30% of patients who received RYBREVANT. Serious adverse reactions in ≥ 2% of patients included pulmonary embolism, pneumonitis, dyspnea, back pain, and muscular weakness. Adverse reactions resulting in permanent discontinuation of RYBREVANT in ≥ 1% of patients were pneumonia, IRR, pneumonitis, and pleural effusion.

Dose reductions due to an adverse reaction occurred in 15% of patients who received RYBREVANT. Adverse reactions requiring dose reductions in ≥ 2% of patients included dermatitis acneiform, and paronychia.

Grade 5 treatment-emergent adverse events, irrespective of relatedness to RYBREVANT, were reported in 7.0% of patients. The most common events were pneumonia and dyspnea.

Table 12 presents adverse reactions reported in ≥5% of patients treated with RYBREVANT in CHRYSALIS. There were no new safety signals observed with longer term follow-up and additional patients, and therefore no meaningful changes occurred in the safety profile of RYBREVANT.

Table 12: Adverse reactions in CHRYSALIS Reported in ≥5% of Patients

System Organ Class Adverse Reaction	RYBREVANT Exon 20 Ins Prior Chemotherapy (RP2D) (N=129)	
	All Grades(%)	Grade 3-4*(%)
Eye disorders		
Eye disorder [a]	9.3	0
Gastrointestinal disorders		
Stomatitis [b]	26.4	0.8
Nausea	24.0	0
Constipation	23.3	0
Diarrhoea	14.7	3.1
Vomiting	13.2	0
Abdominal pain [c]	9.3	0.8
General disorders and administration site conditions		
Fatigue [d]	32.6	2.3
Oedema [e]	26.4	0.8
Pyrexia	13.2	0
Infections and infestations		
Paronychia	49.6	3.1
Pneumonia	7.8	0.8
Injury, poisoning and procedural complications		
Infusion related reaction	64.3	3.1
Investigations		
Alanine aminotransferase increased	17.1	0.8
Aspartate aminotransferase increased	13.2	0
Blood alkaline phosphatase increased	9.3	0.8
Gamma-glutamyltransferase increased	6.2	0.8
Metabolism and nutrition disorders		
Hypoalbuminemia [f]	32.6	3.1
Decreased appetite	14.7	0
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain [g]	45.0	0
Nervous system disorders		
Dizziness [h]	10.1	0.8

System Organ Class Adverse Reaction	RYBREVANT Exon 20 Ins Prior Chemotherapy (RP2D) (N=129)	
	All Grades(%)	Grade 3-4*(%)
Paraesthesia	8.5	0
Headache	6.2	0.8
Respiratory, thoracic and mediastinal disorders		
Dyspnea	19.4	0.8
Cough	13.2	0
Skin and subcutaneous tissue disorders		
Rash [i]	82.2	3.9
Pruritus	16.3	0
Dry skin [j]	15.5	0
Skin fissures	8.5	0

*No Grade 4 events observed
RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Adverse events were coded using MedDRA version 23.0.
Note: Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
[a] includes Blepharitis, Conjunctival hyperaemia, Corneal irritation, Dry eye, Eye pruritus, Growth of eyelashes, Keratitis, Ocular hyperaemia, Uveitis, Vision blurred, Visual acuity reduced, Visual impairment
[b] includes Aphthous ulcer, Cheilitis, Glossitis, Mouth ulceration, Mucosal inflammation, Stomatitis
[c] includes Abdominal pain, Abdominal pain lower, Abdominal pain upper, Epigastric discomfort
[d] includes Asthenia, Fatigue
[e] includes Eyelid oedema, Face oedema, Generalised oedema, Oedema, Oedema peripheral, Periorbital oedema, Peripheral swelling
[f] includes Blood albumin decreased, Hypoalbuminaemia
[g] includes 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.
[h] includes Dizziness
[i] includes Acne, Dermatitis, Dermatitis acneiform, Palmar-plantar erythrodysaesthesia syndrome, Perineal rash, Rash, Rash erythematous, Rash maculo-papular, Rash papular, Rash vesicular, Skin exfoliation
[j] includes Dry skin, Eczema, Eczema asteatotic

8.3 Less Common Clinical Trial Adverse Reactions

Previously Treated NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations

The following are clinically significant TEAEs reported in <5% of RYBREVANT-treated patients with NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations in MARIPOSA-2:

Musculoskeletal and connective tissue disorders: myalgia

Respiratory, thoracic and mediastinal disorders: Interstitial lung disease/Pneumonitis (see 7 Warnings and Precautions, Respiratory).

First-line Treatment of NSCLC with EGFR Exon 20 Insertion Mutations

The following are clinically significant TEAEs reported in <5% of patients receiving RYBREVANT in the PAPILLON Study:

Infections and infestations: Skin infection

Respiratory, thoracic and mediastinal disorders: Interstitial lung disease/Pneumonitis (see 7 Warnings and Precautions, Respiratory); Epistaxis

Previously Treated NSCLC with EGFR Exon 20 Insertion Mutations

The following are clinically significant adverse reactions reported in <5% of patients receiving RYBREVANT in the CHRYSALIS Study:

Respiratory, thoracic and mediastinal disorders: Interstitial lung disease (ILD) (see 7 Warnings and Precautions, Respiratory).

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis (TEN) (see 7 Warnings and Precautions, Skin).

Interstitial lung disease or ILD-like adverse reactions have been reported with the use of RYBREVANT as well as with other EGFR inhibitors.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Previously Treated NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations

Table 13 summarizes the laboratory abnormalities in MARIPOSA-2.

Table 13: Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients With NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations Treated With RYBREVANT in Combination with Carboplatin and Pemetrexed in MARIPOSA-2

Laboratory Abnormality	RYBREVANT + Carboplatin + Pemetrexed (N=130)		Carboplatin + Pemetrexed (N=243)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
Decreased Albumin	73	4	26	<1
Decreased Sodium	48	11	30	6
Increased Aspartate Aminotransferase	47	1	52	1
Increased Alkaline Phosphatase	42	0	29	<1
Increased alanine aminotransferase	39	4	56	6
Decreased Magnesium	38	1	17	<1
Decreased Potassium	37	11	12	3
Increased Gamma Glutamyl Transferase	30	3	41	1
Decreased Calcium (Corrected)	25	0	11	1
Hematology				
Decreased White Blood Cell	90	42	85	19
Decreased Neutrophil Count	74	49	64	25
Decreased Platelet Count	74	17	58	9
Decreased Hemoglobin	71	12	77	9
Decreased Lymphocyte Count	69	28	58	18

First-line Treatment of NSCLC with EGFR Exon 20 Insertion Mutations

Laboratory abnormalities in PAPILLON are summarized in Table 14.

Table 14: Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients With NSCLC with EGFR Exon 20 Insertion Mutations Treated with RYBREVANT in Combination with Carboplatin and Pemetrexed in PAPILLON

Laboratory Abnormality	RYBREVANT + Carboplatin + Pemetrexed[+]		Carboplatin + Pemetrexed	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
Albumin Decreased	87	7	34	1
Aspartate Aminotransferase Increased	60	1	61	1
Alanine Aminotransferase Increased	57	4	54	1
Sodium Decreased	55	7	39	4

Laboratory Abnormality	RYBREVANT + Carboplatin + Pemetrexed[+]		Carboplatin + Pemetrexed	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Alkaline Phosphatase Increased	51	1	28	0
Potassium Decreased	44	11	17	1
Magnesium Decreased	39	2	30	1
Gamma-glutamyltransferase Increased	38	4	43	4
Calcium (Corrected) Decreased	27	1	18	1
Hematology				
White Blood Cells Decreased	89	17	76	10
Hemoglobin Decreased	79	11	85	13
Neutrophils Decreased	76	36	61	23
Platelets Decreased	70	10	54	12
Lymphocytes Decreased	61	11	49	13

Previously Treated NSCLC with EGFR Exon 20 Insertion Mutations

Laboratory abnormalities in CHRYSALIS are summarized in Table 15.

Table 15: Laboratory Abnormalities (≥10%) Worsening from Baseline in Patients Who Received RYBREVANT in CHRYSALIS

Laboratory Abnormality	RYBREVANT (N=129)	
	Change from Baseline All Grades (%)	Change from Baseline Grade 3 or 4 (%)
Chemistry		
Albumin Decreased	79	8
Glucose Increased	56	4
Alkaline Phosphatase Increased	53	5
Creatinine Increased	46	0
Alanine Aminotransferase Increased	38	2
Phosphates Decreased	33	8
Aspartate Aminotransferase Increased	33	0
Gamma-glutamyltransferase Increased	27	4
Magnesium Decreased	27	0
Sodium Decreased	27	4
Potassium Decreased	26	6
Potassium Increased	14	1
Glucose Decreased	12	0
Hematology		
Lymphocyte Count Decreased	36	8
Hemoglobin Decreased	18	2
Neutrophil Count Decreased	18	3
Platelet Count Decreased	17	1
White Blood Cell Decreased	17	2

Laboratory Abnormality	RYBREVANT (N=129)	
	Change from Baseline All Grades (%)	Change from Baseline Grade 3 or 4 (%)
Note: Denominator used to calculate the rate is the number of patients with a baseline value and at least one post-treatment value for the specific lab test		

8.5 Post-Market Adverse Reactions

The following adverse reactions associated with the use of RYBREVANT were identified. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: Skin ulcer

9 Drug Interactions

9.2 Drug Interactions Overview

No formal drug interaction studies have been performed.

9.3 Drug-Behavioural Interactions

Drug-behavioural interactions have not been established.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 Clinical Pharmacology

10.1 Mechanism of Action

Amivantamab is a bispecific antibody that binds to the extracellular domains of the EGFR and MET receptors, disrupting EGFR and MET signaling functions through blocking ligand binding and enhancing degradation of these receptors. The presence of EGFR and MET on the surface of tumor cells also allows for targeting of these cells for destruction by immune effector cells, such as natural killer cells and macrophages, through antibody-dependent cellular cytotoxicity (ADCC) and trogocytosis mechanisms, respectively.

10.2 Pharmacodynamics

Pharmacodynamic responses of amivantamab in NSCLC patients with EGFR Exon 20 insertion, Exon 19 deletion, or Exon 21 substitution mutations have not been fully characterized.

10.3 Pharmacokinetics

Amivantamab pharmacokinetics (PK) as monotherapy or in combination with carboplatin and pemetrexed were assessed using non-compartmental analysis (NCA) and population PK. NCA PK parameters corresponding to 1050 mg (< 80 kg) and 1400 mg (≥ 80 kg) are summarized in Table 16. Amivantamab exposure, based on amivantamab monotherapy data and assessed by area under the concentration-time curve (AUC_{1week}), increases proportionally over a dose range from 350 to 1750 mg.

Based on the population pharmacokinetics of RYBREVANT, steady-state concentrations of RYBREVANT were reached by week 13 for both the 3-week and 2-week dosing regimen and the systemic accumulation was 1.9-fold.

10.4 Immunogenicity

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

In clinical trials of patients with locally advanced or metastatic NSCLC treated with RYBREVANT as monotherapy or as part of a combination therapy, 4 of the 1078 (0.4%) of participants who were treated with RYBREVANT and evaluable for the presence of anti-drug antibodies (ADA) tested positive for treatment emergent anti-amivantamab antibodies (one at 27 days, one at 59 days, one at 84 days, and one at 168 days after the first dose) with titers of 1:160 or less. Due to low immunogenicity observed with RYBREVANT, no meaningful conclusions can be made regarding the impact of ADAs on PK, safety (including IRRs), and efficacy.

Table 16: Summary of Amivantamab Pharmacokinetic Parameters following Intravenous Administration as Monotherapy (1050 mg for < 80 Kg or 1400 mg for ≥ 80 Kg)

Parameter	C_{max} (mcg/mL) Mean (SD)	T_{max} (h) Median (Min – Max)	AUC_{0-168h} (mcg.h/mL) Mean (SD)
Cycle 1 Day 1[a,b]			
1050 mg (<80 Kg)	385 (89.2)	-	33663 (9424)
1400 mg (≥ 80 Kg)	337 (74.8)	-	28062 (5612)
Cycle 2 Day 1[c]			
1050 mg (<80 Kg)	836 (264)	4.08 (2.03-8.33)	94946 (35440)
1400 mg (≥ 80 Kg)	655 (109)	5.72 (2.28-25.47)	76946 (14557)

[a] For 1050 (< 80 Kg) mg, n=24 for AUC_{0-168h} and n=23 for C_{max}. For 1400 (≥ 80 Kg) mg, n=8 for AUC_{0-168h} and C_{max}.
[b] Due to the split dose administration between Day 1 and Day 2, Tmax was not reported for at C1D1.
[c] For 1050 (< 80 Kg) mg, n=26 for C_{max} and T_{max} and n=25 for AUC_{0-168h}. For 1400 (≥ 80 Kg) mg, n=13 for C_{max} and T_{max} and n=12 for AUC_{0-168h}.

Distribution

Amivantamab mean ± SD volume of distribution estimated from population pharmacokinetic (PK) parameters was 5.34 ± 1.81 L.

Elimination

The geometric mean (% CV) linear clearance (CL) and terminal half-life are 0.266 L/day (30.4%), and 13.7 days (31.9%), respectively.

Special populations and conditions

No clinically meaningful differences in the pharmacokinetics of amivantamab were observed based on age (27-87 years). The clearance of amivantamab was 24% higher in males than in females. The population PK analysis estimated that amivantamab exposure was 35% higher in women than in men at steady state; however, no clinically meaningful differences were observed based on gender.

- **Pediatrics (<18 years):** The pharmacokinetics of amivantamab in pediatric patients have not been investigated.
- **Hepatic Insufficiency:** No clinically meaningful difference in the pharmacokinetics of amivantamab was observed in patients with mild hepatic impairment [(total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5 x ULN)]. The pharmacokinetics of amivantamab have not been studied in patients with moderate (total bilirubin 1.5 to 3 times ULN) or severe (total bilirubin > 3 times ULN) hepatic impairment.
- **Renal Insufficiency:** No clinically meaningful difference in the pharmacokinetics of amivantamab was observed in patients with mild (60 ≤ creatinine clearance [CrCl] < 90 mL/min) or moderate (29 ≤ CrCl < 60 mL/min) renal impairment. The pharmacokinetics

of amivantamab have not been studied in patients with severe renal impairment (15 ≤ CrCl < 29 mL/min).

- **Body Weight:** Amivantamab volume of distribution and clearance increased with increasing body weight. Amivantamab exposures were 30-40% lower in patients who weighed ≥ 80 kg compared to patients with a body weight < 80 kg when given the same dose. At the recommended dose of amivantamab, 1050 mg for patients with a body weight < 80 kg and 1400 mg for patients with a body weight ≥ 80 kg, the amivantamab exposures were comparable.

11 Storage, Stability, and Disposal

Unopened vial:

Store in a refrigerator at 2°C to 8°C. Do not freeze. Store in the original carton in order to protect from light.

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.

12 Special Handling Instructions

Do not freeze. Protect from light. This product contains no preservative. Any unused medicinal product should be disposed of in accordance with local requirements.

Part 2: Scientific Information

13 Pharmaceutical Information

Drug Substance

Proper name: Amivantamab

Molecular mass: Approximately 148 kDa

Structure: Amivantamab is a low-fucose, fully human, bispecific Immunoglobulin G1 based bispecific antibody directed against the epidermal growth factor (EGF) and mesenchymal-epithelial transition (MET) receptors.

Physicochemical properties: RYBREVANT (amivantamab for injection) is available as a colorless to pale yellow preservative-free liquid concentrate for intravenous infusion after dilution.

Product Characteristics: Amivantamab is produced by a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology (see 10.1 Mechanism of Action).

14 Clinical Trials

14.1 Clinical Trials by Indication

Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) with EGFR Mutations

Previously Treated NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations

Table 17: Summary of Patient Demographics for MARIPOSA-2 clinical trial (NSC3002) in patients with previously treated NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (range)	Sex
NSC3002 (MARIPOSA-2)	Phase 3, randomized, open label, multicentre study	**RYBREVANT**: 1400 mg, <80 kg body weight, or 1750 mg, ≥80 kg body weight IV, once weekly through 4 weeks. <u>Starting at Week 7</u> 1,750 mg, < 80 kg body weight, or 2,100 mg, ≥ 80 kg body weight IV, once every 3 weeks until disease progression or unacceptable toxicity. **Carboplatin**: AUC 5*, IV, once every 3 weeks for up to 12 weeks. **Pemetrexed:** 500 mg/m^2, IV, once every 3 weeks until disease progression or unacceptable toxicity.	N=394 RYBREVANT + carboplatin+ pemetrexed n=131 carboplatin+ pemetrexed n=263	62 years (31-85)	Female: 60.4% Male: 39.6%

*AUC5 = area under the concentration-time curve 5 mg/mL per minute

The efficacy of RYBREVANT was evaluated in patients with locally advanced or metastatic NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations (characterized by a validated test at or after the time of locally advanced or metastatic disease diagnosis, as identified by local or central testing) who had previously received osimertinib as first or second line therapy in MARIPOSA-2, an open-label, multicenter phase 3 clinical trial. In MARIPOSA-2, patients were randomised (2:2:1) to receive carboplatin and pemetrexed (CP, N=263), RYBREVANT in combination with carboplatin and pemetrexed (RYBREVANT-CP, N=131) and RYBREVANT in combination with lazertinib, carboplatin, and pemetrexed (N=263) in a separate arm of the study (an unapproved regimen for EGRFm NSCLC).

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

The primary efficacy endpoint was progression-free survival (PFS) as assessed by blinded independent central review (BICR) using RECIST 1.1. Secondary efficacy endpoints were objective response rate (ORR) and overall survival (OS). PFS and ORR were evaluated at the first interim analysis. There are two interim, and one final analysis planned for OS.

Of the 394 patients randomized to the RYBREVANT-CP arm or CP arm, the median age was 62 (range: 31–85) years, with 37.8% of the patients ≥ 65 years of age; 60.4% were female; and 48.2% were Asian and 46.4% were White. Baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 (39.6%) or 1 (60.4%); 65.5% never smoked; 45.2% had history of brain metastasis, and 91.6% had Stage IV cancer at initial diagnosis. Osimertinib had been given as first-line systemic therapy for 70.5% of participants and second-line therapy for 29.4% of participants.

Study Results

Efficacy results are summarized in Table 18 and Figure 1

Table 18: Efficacy results in MARIPOSA-2

	RYBREVANT + Carboplatin + Pemetrexed (N=131)	**Carboplatin + Pemetrexed (N=263)**
Progression-free survival (PFS)[a]		
Number of events (%)	74 (56.5%)	171 (65.0%)
Median, months (95% CI)	6.28 (5.55, 8.41)	4.17 (4.04, 4.44)
HR (95% CI); p-value	0.48 (0.36, 0.64); p<0.0001	
Objective response rate[a]		
ORR, % (95% CI)	63.8% (55.0, 72.1)	36.2% (30.3, 42.3)
Complete response	1.5%	0.4%
Partial response	62.3%	35.8%

CI = confidence interval

[a] Blinded Independent Central Review by RECIST v1.1

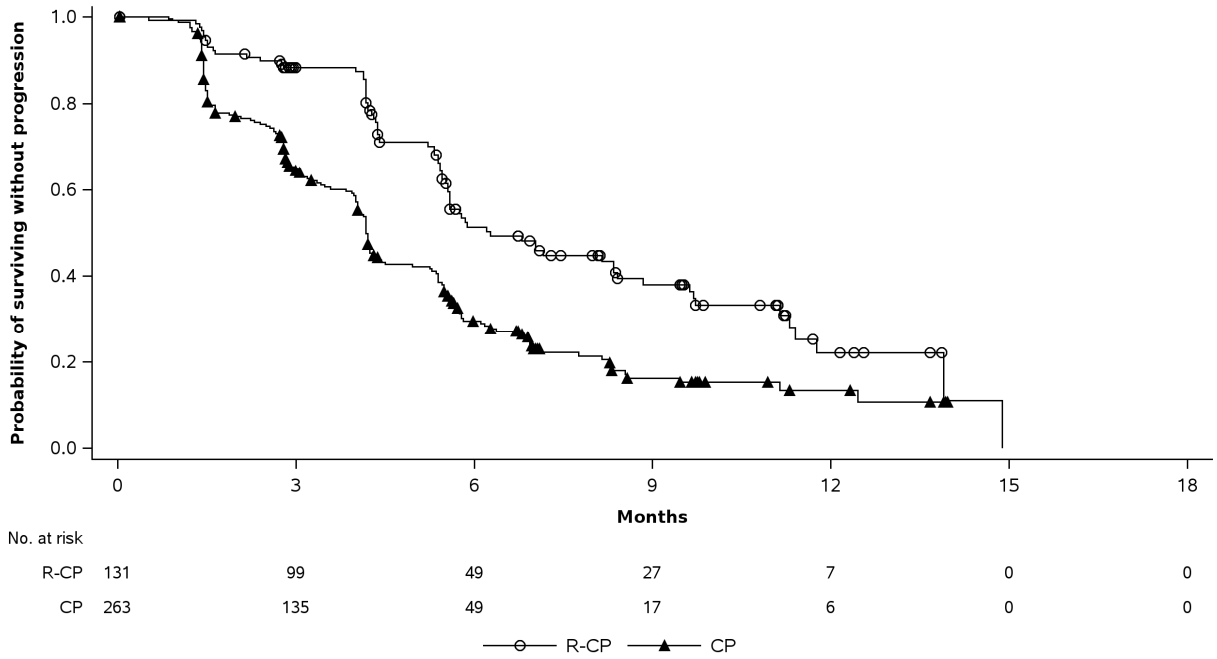

Figure 1: Kaplan-Meier curve of PFS in Previously Treated NSCLC Patients by BICR assessment - MARIPOSA-2

The median duration of response was 6.90 months (95% CI: 5.52, NE months) for patients who received RYBREVANT plus carboplatin and pemetrexed and 5.5 months (95% CI: 4.17, 9.56 months) for patients treated with carboplatin and pemetrexed alone.

The estimated OS HR at the first interim analysis was 0.77 [95% CI: 0.49, 1.21], however OS remains immature at the time of this analysis.

Patients with asymptomatic or previously treated and stable intracranial metastases were eligible to be randomized in MARIPOSA-2. In an exploratory sub-group analysis, in patients with stable intracranial metastases, the observed median intracranial PFS for RYBREVANT-CP was 12.45 months vs 8.31 months in the CP arm; HR=0.55 (95%CI 0.38, 0.79).

First-line Treatment of NSCLC with EGFR Exon 20 Insertion Mutations

Table 19: Summary of patient demographics for the PAPILLON clinical trial (NSC3001) in patients with previously untreated NSCLC with Exon 20ins mutations

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
PAPILLON: NSC3001	Phase 3, randomized, open label, multicentre study	**RYBREVANT**: 1400 mg, <80 kg body weight, or 1750 mg, >80 kg body weight IV, once weekly through 4 weeks. <u>Starting at Week 7</u> 1,750 mg, < 80 kg body weight, or 2,100 mg, ≥ 80 kg body weight IV, once every 3 weeks until disease progression or unacceptable toxicity. **Carboplatin**: AUC 5*, IV, once every 3 weeks for up to 12 weeks. **Pemetrexed:** 500 mg/m^2, IV, once every 3 weeks until disease progression or unacceptable toxicity.	N=308 RYBREVANT+ carboplatin+ pemetrexed n=153 carboplatin+ pemetrexed n=155	62 years (27-92)	Female: 58% Male: 42%

*AUC5 = area under the concentration-time curve 5 mg/mL per minute

PAPILLON (NSC3001) is a randomized, open-label, multicenter phase 3 study comparing treatment with RYBREVANT in combination with carboplatin and pemetrexed to treatment as compared to chemotherapy alone (carboplatin and pemetrexed) in subjects with treatment-naïve, locally advanced or metastatic NSCLC with EGFR Exon 20 insertion mutations, as identified prospectively by local testing.

Patients with squamous NSCLC, untreated brain metastases, with a medical history of ILD, or any evidence of clinically active ILD were excluded from the clinical study.

Randomization was stratified by ECOG performance status and prior brain metastases.

The primary efficacy outcome measure was progression-free survival (PFS) as assessed by blinded independent central review (BICR) using RECIST 1.1. Secondary efficacy outcome

measures were objective response rate (ORR) and overall survival (OS). Subjects randomized to the carboplatin and pemetrexed arm who had confirmed disease progression were permitted to cross over to receive RYBREVANT monotherapy.

A total of 308 subjects were randomized (1:1) to RYBREVANT in combination with carboplatin and pemetrexed (N=153) or carboplatin and pemetrexed (N=155). The median age was 62 (range: 27 to 92) years, with 39% of the subjects ≥ 65 years of age; 58% were female; and 61% were Asian and 36% were White. Baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 (35%) or 1 (65%); 58% never smoked; 23% had history of brain metastasis and 84% had Stage IV cancer at initial diagnosis (99% had Stage IV cancer at screening).

Study Results

The median follow-up time at the time of the PFS analysis was 14.9 (range: 0.3 to 27.0) months.

Efficacy results for PAPILLON are summarized in Table 20 and Figure 2.

Table 20: Efficacy Results in PAPILLON

	RYBREVANT+ carboplatin+ pemetrexed (N=153)	**Carboplatin+ pemetrexed (N=155)**
Progression-free survival (PFS) [a]		
Number of events (%)	84 (55%)	132 (85%)
Median, months (95% CI)	11.4 (9.8, 13.7)	6.7 (5.6, 7.3)
HR (95% CI); p-value[b]	0.40 (0.30, 0.53); p<0.0001	
Objective response rate (ORR)[a,c]		
ORR, % (95% CI)	73% (65%, 80%)	47% (39%, 56%)
p-value[d]	p<0.0001	
Complete response	3.9%	0.7%
Partial response	69%	47%

CI = confidence interval

[a] Blinded Independent Central Review by RECIST v1.1

[b] p-value is from a log-rank test stratified by ECOG PS (0 or 1) and history of brain metastases (yes or no).

[c] Including Unconfirmed Response.

[d] p-value is from a logistic regression model stratified by ECOG PS (0 or 1) and history of brain metastases (yes or no).

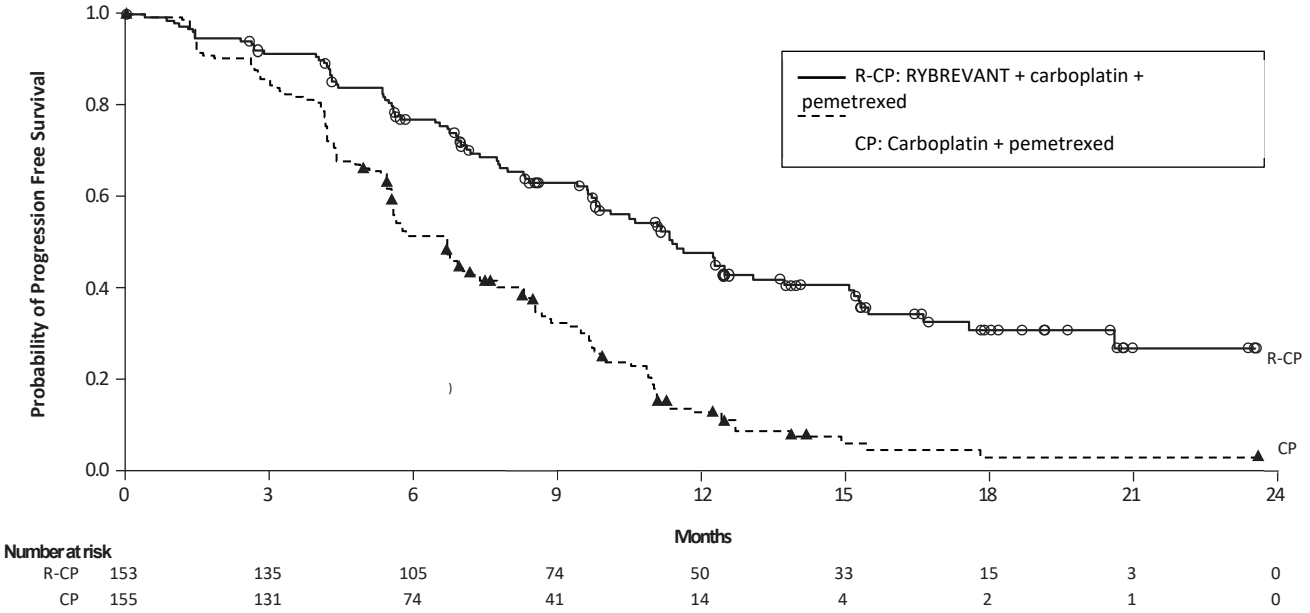

Figure 2: Kaplan-Meier Curve of PFS in Previously Untreated NSCLC Patients by BICR Assessment

The objective response rate (ORR) for patients who had a confirmed response was 67.1% for patients who received RYBREVANT plus carboplatin and pemetrexed and 36.2% for patients treated with carboplatin and pemetrexed alone. For patients who achieved a confirmed objective response, the median duration of response was 10.1 months (range: 1.4 to 22.3 months) for patients who received RYBREVANT plus carboplatin and pemetrexed and 5.6 months (range: 1.3 to 22.4 months) for patients treated with carboplatin and pemetrexed alone.

At this PFS analysis, 65 (42%) patients who were randomized to the carboplatin and pemetrexed arm had crossed over to receive subsequent RYBREVANT monotherapy. At the prespecified first interim analysis for overall survival (OS), conducted at the time of the primary analysis of PFS, statistical significance had not been reached (HR=0.72 [95% CI: 0.44, 1.17]).

Previously Treated NSCLC with EGFR Exon 20 insertion mutations

Table 21: Summary of patient demographics for the CHRYSALIS clinical trial (EDI1001) in patients with previously treated NSCLC with Exon 20ins mutations

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
CHRYSALIS: EDI1001	Phase 1, open label, single arm, multi-cohort study	1050 mg, <80 kg body weight 1400 mg, >80 kg body weight IV, once weekly in cycle 1; bi-weekly thereafter	N=81 (efficacy population)	62 years (42-84)	Female: 48 Male: 33

CHRYSALIS (EDI1001) was a multicenter, 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 81 patients with locally advanced or metastatic NSCLC who had EGFR Exon 20 insertion mutation, with measurable disease, whose disease had progressed on or after platinum-based chemotherapy. For enrollment, EGFR exon 20 insertion mutation status was determined prospectively by local testing using tissue and/or plasma 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. The median follow-up for the efficacy population was 9.7 months.

RYBREVANT was administered intravenously at 1050 mg for patients < 80 kg or 1400 mg for patients ≥ 80 kg once weekly for 4 weeks, then every 2 weeks starting at Week 5 until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by Blinded Independent Central Review (BICR). Duration of response (DOR) by BICR was assessed as an additional measure of efficacy.

The median age was 62 (range: 42–84) years, with 9% of the patients ≥75 years of age; 59% were female; and 49% were Asian and 37% were White; 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 therapies). At baseline, 99% had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; 53% never smoked; 75% had Stage IV cancer; and 22% had previous treatment for brain metastases. Insertions in Exon 20 were observed at 8 different residues; the most common residues were A767 (24%), S768 (16%), D770 (11%), and N771 (11%).

Study Results

Efficacy results are summarized in Table 22.

Table 22: Results from CHRYSALIS: Patients with EGFR Exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy

	Prior Platinum Chemotherapy Treated (N=81)
Overall Response Rate [a,b] (95% CI)	40% (29%, 51%)
Complete response (%)	3.7%
Partial response (%)	35.8%
Duration of Response [a] **(DOR)**	
Median (95% CI), months [c]	11.1 (6.9, NE)
Patients with DOR ≥ 6 months	63%

[a] Blinded Independent Central Review by RECIST v1.1
[b] Confirmed response.
[c] Based on Kaplan-Meier estimate.
NE=Not Estimable

15 Microbiology

No microbiological information is required for this product.

16 Non-Clinical Toxicology

General toxicology: In repeat-dose toxicity studies in cynomolgus monkeys, amivantamab was well-tolerated at weekly doses up to 120 mg/kg intravenously for 3 months and up to 125 mg/kg subcutaneously for 2 weeks. 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.

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

Genotoxicity: Routine genotoxicity studies are generally not applicable to biologic pharmaceuticals as large proteins cannot diffuse into cells and cannot interact with DNA or chromosomal material.

Reproductive and developmental toxicology: No long-term animal studies have been performed to evaluate whether amivantamab affects fertility in males or females or reproduction.

Based on its mechanism of action, amivantamab could cause fetal harm or developmental abnormalities when administered to a pregnant woman. Evidence from published literature showed that inhibition of EGFR and/or MET signaling pathways during pregnancy can cause impaired embryo-fetal development, embryo lethality and abortions in mice, rats and non-human primates. Therefore, it is reasonable to expect that amivantamab may cause adverse effects on embryo-fetal and postnatal development in humans.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrRYBREVANT®

amivantamab for injection

50 mg/mL Concentrate for Solution for Infusion

This Patient Medication Information is written for the person who will be taking **RYBREVANT**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about RYBREVANT, talk to a healthcare professional.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

What RYBREVANT is used for:

- See the following boxed text

RYBREVANT is used in adults with a type of cancer called 'non-small cell lung cancer'. It is used when the cancer has spread in your body and has gone through certain genetic changes (EGFR Exon 19 deletions, Exon 21 L858R substitution mutations, or Exon 20 insertion mutations) in a gene called 'epidermal growth factor receptor' (EGFR).

For the following indication, RYBREVANT has been approved **with conditions (NOC/c)**. This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to verify RYBREVANT's clinical benefit. For more information, talk to your healthcare professional.

RYBREVANT can be prescribed for you:

- after chemotherapy stops working against your cancer.

For the following indications, RYBREVANT has been approved **without conditions**. This

means it has passed Health Canada's review and can be bought and sold in Canada.

RYBREVANT can be prescribed for you:

- in combination with chemotherapy after osimertinib stops working against your cancer.
- as the first medicine you receive for your cancer in combination with chemotherapy.

How RYBREVANT works:

Amivantamab is an antibody, that is a type of protein, that has been designed to recognise and attach to specific targets in the body. Amivantamab targets two proteins found on cancer cells:

- Epidermal growth factor receptor (EGFR), and
- Mesenchymal-epithelial transition factor (MET).

RYBREVANT 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.

RYBREVANT may be given in combination with other anti-cancer medicines. It is important that you also read the package leaflets for these other medicines. If you have any questions about these medicines, ask your doctor.

The ingredients in RYBREVANT are:

Medicinal ingredients: Amivantamab

Non-medicinal ingredients: Ethylenediaminetetraacetic acid (EDTA), L-histidine, L-methionine, polysorbate 80, sucrose, and water for injection

RYBREVANT comes in the following dosage forms:

Liquid concentrate for intravenous infusion, 350 mg / 7 mL vial

Do not use RYBREVANT if:

- you are allergic to amivantamab or any other ingredients of RYBREVANT (see "The ingredients in RYBREVANT are:")

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RYBREVANT. Talk about any health conditions or problems you may have, including if you:

- have a history of lung or breathing problems
- have suffered from inflammation of your lungs (a condition called "interstitial lung disease" or "pneumonitis")

Other warnings you should know about:

Infusion related reactions: Before each infusion of RYBREVANT, you will be given medicines which help to 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 acetaminophen)

You may also be given additional medicines based on any symptoms you may experience. If you have any further questions on the use of this medicine, ask your doctor or nurse.

Tell your healthcare professional straight away while taking RYBREVANT if you get any of the following side effects:

- Any side effect during the intravenous infusion (drip into a vein) of RYBREVANT.
- Sudden difficulty in breathing (shortness of breath), cough, or fever that may suggest inflammation of the lungs.
- Skin and nail 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 RYBREVANT. You also need to do 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

RYBREVANT should not be given to children or young people below 18 years of age. This is because it is not known how the medicine will affect them.

Contraception

If you or your partner could become pregnant, you must use effective contraception during and for 3 months after stopping treatment with RYBREVANT.

Pregnancy and fertility – information for women

Tell your doctor or nurse before you are given RYBREVANT if you are pregnant, think you might be pregnant or are planning to have a 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 baby.

Pregnancy and fertility – information for men

If your partner becomes pregnant while you are taking this medicine, tell your doctor straight away.

Men should not donate or store semen during and for 3 months after stopping treatment with RYBREVANT.

Breast-feeding

You should not breast-feed while taking this medicine and for 3 months after stopping treatment with RYBREVANT.

Driving and using machines

If you feel tired or feel dizzy after taking RYBREVANT, do not drive or use machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Interactions with other drugs, vitamins, minerals, natural supplements or alternative medicines have not been established with RYBREVANT.

How you are given RYBREVANT:

- RYBREVANT will be given to you by a healthcare professional in a healthcare setting.
- A nurse or doctor will give you RYBREVANT through a drip into a vein ('intravenous infusion') over several hours.

Usual dose:

Your doctor will determine your dose of RYBREVANT. The dose of RYBREVANT will depend on your body weight at the start of your therapy. In the first week your doctor will give you the RYBREVANT dose split over two days.

The usual dose of RYBREVANT when given alone is:

- 1050 mg if you weigh less than 80 kg (175 lbs).
- 1400 mg if you weigh more than or equal to 80 kg (175 lbs).

When given alone, RYBREVANT is given as follows:

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

The usual dose of RYBREVANT when given with chemotherapy, is:

- 1400 mg for the first 4 doses and 1750 mg for subsequent doses if you weigh less than 80 kg (175 lbs).
- 1750 mg for the first 4 doses and 2100 mg for subsequent doses if you weigh more than or equal to 80 kg (175 lbs).

When given with chemotherapy, RYBREVANT is given as follows:

- once a week for the first 4 weeks
- then once every 3 weeks starting at Week 7 as long as you are getting benefit from the treatment.

<u>Other medicines given before treatment with RYBREVANT</u>

You will be given other medicines that help to lower the chance of infusion-related reactions.

Two days before the first infusion of RYBREVANT

- Oral medicines for inflammation (Corticosteroids)

Day of Infusion of RYBREVANT

- medicines for an allergic reaction (anti-histamines)
- medicines for inflammation (corticosteroids)
- medicines for fever (such as acetaminophen)

Overdose:

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 think you, or a person you are caring for, have taken too much RYBREVANT, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

If you miss an appointment to get RYBREVANT:

- If you miss an appointment, call your doctor and make another appointment as soon as possible
- It is very important to go to all of your appointments

Possible side effects from using RYBREVANT:

These are not all the possible side effects you may have when taking RYBREVANT. If you experience any side effects not listed here, tell your healthcare professional.

Very common side effects (may affect more than 1 in 10 people (>10%)

- Rash
- Infected skin around the nail
- Dry skin
- Itching
- Constipation or diarrhoea
- Sores in mouth
- Nausea or vomiting
- Feeling very tired
- Swollen hands, face, ankles or feet
- Decreased appetite
- Dizziness
- Fever
- Changes in eyesight

- Muscle pain
- Cough
- Shortness of breath

Common side effects (may affect between 1 and 10 people out of every 100)

- Hemorrhoids
- Stomach pain
- Muscle aches and joint pain

RYBREVANT can cause abnormal blood tests. Your doctor will decide when to perform blood tests and will interpret the results. RYBREVANT may cause:

- low level of 'albumin' in the blood
- increased level of liver enzymes 'alanine aminotransferase', 'aspartate aminotransferase', and 'gamma-glutamyltransferase' in the blood
- low level of sodium in the blood
- low number of white blood cells
- low number of red blood cells
- low number of platelets, cells that help blood to clot
- high level of 'bilirubin' in the blood
- low level of phosphate in the blood
- low level of protein in the blood
- high level of sugar in the blood
- increased level of blood lactate dehydrogenase
- increased level of 'creatinine' in the blood

Serious side effects and what to do about them

Frequency/Symptom /effect	Talk to your healthcare professional	
	Only if severe	**In all cases**
Very common (affecting more than 1 in 10 people)		
Infusion reactions: chills, nausea, feeling short of breath, flushing, chest discomfort, vomiting, or any side effect during an infusion. This can happen especially with the first dose.		**√**
Skin and Nail Problems: rash (including acne), infected skin around the nails, dry skin, itching, pain, blistering, and redness. Tell your doctor if your skin or nail problems get worse.		**√**
Eye Problems: dry eye, eye redness, itchy eyes, problems/changes with vision, growth of eyelashes, inflamed cornea (front part of the eye), excessive tearing		**√**

Frequency/Symptom /effect	Talk to your healthcare professional	
	Only if severe	In all cases
Common (affecting between 1 to 10 people out of every 100)		
Inflammation of the lungs: sudden difficulty in breathing, cough, or fever. This could lead to permanent damage ('interstitial lung disease')		√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

RYBREVANT will be stored at a hospital or clinic.

Store in a refrigerator at 2°C to 8°C. Do not freeze. Protect from light.

If you want more information about RYBREVANT:

- Talk to your healthcare professional
- For questions or concerns, please contact the manufacturer, Janssen Inc., at innovativemedicine.jnj.com/canada
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (Drug Product Database: Access the database; the manufacturer's website (innovativemedicine.jnj.com/canada), or by calling 1-800-567-3331.

This leaflet was prepared by Janssen Inc., a Johnson & Johnson company.

Toronto, ON, M3C 1L9

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