# Summary Report of Benefit-Risk Assessment

## RYBREVANT CONCENTRATE FOR SOLUTION FOR INFUSION 350MG/7ML

## NEW DRUG APPLICATION

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|---|---|
| **Active Ingredient(s)** | Amivantamab |
| **Product Registrant** | Johnson & Johnson Pte. Ltd. |
| **Product Registration Number** | SIN16548P |
| **Application Route** | Abridged |
| **Date of Approval** | 13 July 2022 |

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## A INTRODUCTION

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

Amivantamab, the active substance contained in Rybrevant, is a fully human immunoglobulin G1 (IgG1)-based bispecific antibody directed against the EGFR and mesenchymal epidermal transition (MET) receptor. Amivantamab is produced by a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology.

Rybrevant is available as a concentrate for solution for infusion containing 350mg/7ml of amivantamab. Other ingredients in the vial are EDTA disodium salt dihydrate, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, Polysorbate 80, sucrose and water for injection.

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## B ASSESSMENT OF PRODUCT QUALITY

The drug substance, amivantamab, is manufactured at Biogen, Inc. North Carolina, USA and Janssen Sciences Ireland UC (JSI), Cork, Ireland. The drug product, Rybrevant Concentrate for Solution for Infusion 350mg/7ml, is manufactured at Cilag AG, Schaffhausen, Switzerland.

**Drug substance:**

Adequate controls have been presented for the starting materials, intermediates, reagents and cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturers are compliant with Good Manufacturing Practice (GMP). Process validation was conducted on four consecutive production-scale batches.

The characterisation of the drug substance and its impurities are appropriately performed. Potential and actual impurities are adequately controlled in the specifications.

The drug substance specifications are established in accordance with ICH Q6B and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been appropriately validated in accordance with ICH Q2 guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented was adequate to support storage at -40 ± 10°C with a shelf life of 24 months. The packaging is a polycarbonate bottle with silicone lined polypropylene screw closure.

**Drug product:**

The manufacturing process utilises aseptic processing.

The manufacturing site involved is compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6B and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support a shelf-life of 24 months when stored between 2 - 8ºC. The in-use period of 10 hours at 15 – 25°C after dilution with 5% dextrose or 0.9% normal saline is supported with in-use stability data. The container closure system is a type 1 glass vial with fluorotec-coated rubber stopper and aluminium seal with a plastic flip off cap.

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## C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of amivantamab in the treatment of patients with locally advanced or metastatic NSCLC with EGFR Exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy was based primarily on a selected subset of patients in the Phase 1 study, Protocol 61186372EDI1001 (CHRYSALIS), referred to as Study EDI1001.

Study EDI1001 is an ongoing, first-in-human, Phase 1, open-label, single-arm, two-part, multicentre study of amivantamab as monotherapy in subjects at least 18 years of age with advanced or metastatic NSCLC. Taking into consideration that this is an early phase study in an advanced refractory cancer setting with no clear global standard of care, the single-arm design is considered acceptable.

Part 1 of the study consisted of the dose escalation phase, conducted in 77 subjects, to determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) for subjects with NSCLC treated with amivantamab for further exploration in Part 2. A dose-escalation 3 + 3 design was used and six pre-planned amivantamab dose cohorts (140 mg, 350 mg, 700 mg, 1050 mg, 1400 mg, and 1750 mg) were administered amivantamab once weekly for the first 4 weeks followed by once every 2 weeks thereafter via intravenous (IV) infusion. After identifying body weight as a primary covariate explaining interindividual pharmacokinetic (PK) variability, the RP2D was determined to be 1050 mg for subjects weighing <80 kg, and 1400 mg for subjects weighing ≥80 kg.

Part 2 of the study consisted of the dose expansion phase, which was conducted in 285 subjects to characterise the safety and PK of amivantamab monotherapy at the RP2D and to explore its clinical activity within molecularly defined tumour subgroups (6 cohorts: cohorts A – D, cohort MET-1 and cohort MET-2) in subjects with locally advanced or metastatic EGFR-mutated NSCLC (EGFR Exon 20ins, third generation tyrosine kinase inhibitor (TKI) resistance mutations, and MET amplification or mutations). Different regimens of amivantamab as monotherapy and in combination with other drugs were investigated. For the current application, the results of amivantamab monotherapy after platinum-based chemotherapy in patients with EGFR Exon 20 insertion mutations were reviewed. Amivantamab was administered via IV infusion (minimum infusion time ≥60 minutes) once weekly for the first 4 weeks (i.e., Cycle 1) and once every 2 weeks thereafter during subsequent 28-day cycles. To

mitigate the risk of infusion-related reactions (IRRs), the first dose of Cycle 1 was split over 2 days (350 mg administered on Cycle 1 Day 1 and the remainder of the dose administered on Cycle 1 Day 2), steroid premedication was required, and the study drug was administered using an accelerated infusion strategy. Thus, study drug administration occurred on Days 1, 2, 8, 15, and 22 of Cycle 1, and on Days 1 and 15 of each subsequent 28-day cycle. Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent.

The primary efficacy endpoint was confirmed overall response rate (ORR), defined as the proportion of subjects who achieved a confirmed complete response (CR) or partial response (PR) using RECIST v1.1 criteria. The null hypothesis would be rejected if the lower bound of 95% two-sided CI of the ORR was above 12% for the Exon 20ins subjects + prior chemotherapy at RP2D efficacy population. Response assessments were performed every 6 (±1) weeks. Responses were confirmed with repeat scans at least 4 weeks after initial documentation of response as required by RECIST version 1.1 criteria. The secondary efficacy endpoints included duration of response (DOR), clinical benefit rate (CBR), progression-free survival (PFS) and overall survival (OS).

The primary population of interest consisted of 114 subjects (data cut-off of 30 March 2021) with EGFR Exon 20 insertion-mutated NSCLC treated at the RP2D who had progressed on or after prior platinum-based chemotherapy (Exon 20ins + prior chemotherapy at RP2D population) and is considered the pivotal efficacy population. The median follow-up was 12.5 months (range: 0.23-30.52). The median age was 62 years (41% aged ≥ 65 years), the majority of subjects were females (61%) and Asian (52%), and 37% of subjects were White. The median number of prior therapies was 2 (range: 1 to 7 therapies). At baseline, 29% had Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 70% had ECOG performance status of 1; 57% never smoked; 100% had Stage IV cancer; and 25% had previous treatment for brain metastases. Insertions in Exon 20 were observed at 8 different residues; the most common residues were A767 (22%), S768 (16%), D770 (12%), and N771 (11%).

Efficacy analyses were also performed on two additional populations: Exon 20ins + no prior chemotherapy at RP2D population (n=24) and Exon 20ins at Non-RP2D population (n=42). These analyses are considered supportive.

**Summary of key efficacy results (pivotal efficacy population)**

| | | | |
|---|---|---|---|
| **Data cut-off date** | 30 March 2021 | | |
| **Analysis description** | Interim Analysis | | |
| **Analysis population and the time point description** | Subjects from Part 1 and Part 2 with EGFR Exon 20 insertion and prior platinum-based chemotherapy, treated with amivantamab monotherapy at RP2D | | |
| **Descriptive statistics and estimate variability** | | Primary analysis by investigator assessment (INV) | Sensitivity analysis by blinded independent central review (BICR) |
| | Treatment group | Amivantamab | Amivantamab |
| | Number of subjects | 114 | 114 |
| | ORR (%) | 36.8% | 43.0% |
| | 95% CI | (28.0%, 46.4%) | (33.7%, 52.6%) |
| | Confirmed CR and PR (%) | CR – 0%<br>PR – 36.8% | CR – 2.6%<br>PR – 40.4% |
| | CBR (%) | 75.4% | 73.7% |
| | 95% CI | (66.5%, 83.0%) | (64.6%, 81.5%) |
| | Median DOR (months) | 12.5 | 10.8 |

| | | | |
|---|---|---|---|
| | 95% CI | (6.5, 16.1) | (6.9, 15.0) |
| | Patients with DOR ≥ 6 months (%) | 64.3% | 55.1% |
| | Median PFS (months) | 6.9 | 6.7 |
| | 95% CI | (5.6, 8.6) | (5.5, 9.7) |
| | OS (months, median) | 22.8 | |
| | 95% CI | (17.5, NE) | |

EGFR: Epidermal growth factor receptor; RP2D: Recommended Phase 2 dose; INV: Investigator; BICR: Blinded Independent Central Review; ORR: Overall response rate; CI: Confidence interval; CR: Complete response; PR: Partial response; DOR: Duration of response; PFS: Progression-free survival; OS: Overall survival; NE: Non estimable

In the pivotal efficacy population, the primary endpoint of overall ORR by investigator (INV) was 36.8% (95% CI: 28.0%, 46.4%) at the cut-off date of 30 March 2021. The ORR sensitivity analysis by BICR showed an ORR of 43.0% (95% CI: 33.7%, 52.6%). Taking into consideration that the ORRs for NSCLC EFGR Exon 20insertion-mutated subgroups from the clinical trials of other drugs are reported to be not more than 20%, the size of the treatment effect (ORR of 37%) in second-line patients with NSCLC EFGR Exon 20insertion mutations was considered reasonable.

Subgroup analysis of ORR by INV was overall consistent across subgroups, ranging from 32% to 48% demonstrating robustness of the data. The ORR by BICR in the same subgroups ranged from 33 to 55% compared to the overall BICR ORR of 43%.

The secondary endpoint of median DOR was 12.5 months (95% CI: 6.5, 16.1) by INV, and 10.8 months (95% CI: 6.9, 15.0) by BICR. The DOR of 12 months was considered a clinically relevant length of time under which disease progression is being delayed and symptoms of disease may potentially be alleviated. The proportion of subjects with DOR ≥ 6 months were 64.3% by INV and 55.1% BICR. Median PFS was 6.9 months (95% CI: 5.6, 8.6) by INV, and 6.7 months (95% CI: 5.5, 9.7) by BICR. Median OS was 22.8 months (95% CI: 17.5, not estimable).

For the two supportive analyses sets from the pivotal study, the ORR as per the initial data cut-off of 08 June 2020 were available. For the Exon 20ins + no prior chemotherapy at RP2D population, the ORR was 37.5% (95% CI: 18.8%, 59.4%), with 9 patients with PR and none with CR. For the Exon 20ins at Non-RP2D population, the ORR was 36.6% (95% CI: 22.1%, 53.1%), with 15 patients with PR and no CR. The ORR in the two supportive data sets from Study EDI1001 (CHRYSALIS) support the results from the pivotal analysis set.

Overall, there were limitations with the early phase single-arm study, which did not allow meaningful conclusions to be made on the clinical benefit of amivantamab in terms of time-to-event endpoints such as PFS and OS. Nevertheless, considering the lack of approved targeted treatment options for the patient population and that the ORR demonstrated with amivantamab compared favourably with historical controls, the available data provided reasonable evidence to support the efficacy of amivantamab in the treatment of patients with EGFR Exon 20 insertion-mutated NSCLC who have received prior chemotherapy.

A Phase 3, randomised, open-label study (Study 61186372NSC3001) comparing amivantamab in combination with carboplatin-pemetrexed therapy vs carboplatin-pemetrexed in advanced or metastatic NSCLC patients with activating EGFR Exon 20 insertion mutations in the first-line treatment setting is ongoing. The final results of this study will be required to confirm the efficacy and safety of amivantamab in the treatment of patients with NSCLC.

## D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of amivantamab was based primarily on data derived from the Phase 1 CHRYSALIS study, comprising a total of 489 patients (referred to as the All Treated population) who received at least one dose of study treatment at the data cut-off of 30 March 2021. Of these, 380 subjects were treated at the RP2D (All Treated at RP2D population) and 153 subjects constituted the target population (Exon 20ins + prior chemotherapy at RP2D population). The median duration of treatment was 4.1 months in the All Treated population and All Treated at RP2D population, and was 5.5 months in the Exon 20ins + prior chemotherapy at RP2D population.

**Overview of safety profile**

| AE | Exon 20ins + prior chemotherapy at RP2D (N=153) | All Treated at RP2D (N=380) | All Treated (N=489) |
|---|---|---|---|
| Any AE | 153 (100.0%) | 378 (99.5%) | 487 (99.6%) |
| Treatment-related AE | 150 (98.0%) | 365 (96.1%) | 471 (96.3%) |
| SAE | 44 (28.8%) | 111 (29.2%) | 141 (28.8%) |
| Treatment-related SAE | 13 (8.5%) | 18 (4.7%) | 27 (5.5%) |
| Discontinuations due to AE | 18 (11.8%) | 26 (6.8%) | 39 (8.0%) |
| Treatment-related discontinuation | 8 (5.2%) | 12 (3.2%) | 21 (4.3%) |
| Deaths due to AE | 11 (7.2%) | 20 (5.3%) | 23 (4.7%) |
| Treatment-related deaths | 0 | 0 | 0 |

Adverse events (AEs) were reported in ≥ 99.5% of subjects and treatment-related AEs in ≥ 96.1% of subjects in all the three study populations. The types of AEs reported with amivantamab were consistent with the known safety concerns seen with EGFR inhibition (rash, nail toxicity, pruritus, dry skin, stomatitis) and MET inhibition (hypoalbuminaemia, peripheral oedema). Other AEs were related to antibody infusion (infusion related reaction or IRR), gastrointestinal disorders (nausea, vomiting, diarrhoea, constipation) and general disorders (pyrexia, fatigue). The AEs of special interest reported with amivantamab included rash, IRR, peripheral oedema and interstitial lung disease (ILD).

Serious adverse events (SAEs) were reported in ≥ 28.8% of the subjects and treatment-related SAEs in ≥ 4.7% subjects in all the three study populations. Discontinuations due to AE were reported in ≥ 6.8% of subjects and treatment-related discontinuations in ≥ 3.2% of subjects in all the three study populations. The frequencies of treatment-related SAEs and discontinuations due to AEs were low, indicating that subjects can continue treatment with amivantamab with appropriate risk management in the clinical setting. The risks associated with amivantamab therapy and their management are described in the package insert in the form of dose modifications including dose reductions and withholding the drug until the AEs improve.

The overall safety and tolerability profiles of amivantamab monotherapy in the All Treated safety population (N=489) and the All Treated at RP2D safety population (N=380) were consistent with that observed for the Exon 20ins + prior chemotherapy at RP2D safety population (N=153).

For the dataset of 380 patients with locally advanced or metastatic NSCLC after failure of platinum-based chemotherapy, who were treated at the RP2D, the most common adverse

reactions in ≥ 20% of the subjects were rash (76%), IRR (67%), nail toxicity (47%), hypoalbuminemia (31%), oedema (26%), fatigue (26%), stomatitis (24%), nausea (23%), and constipation (23%). Serious adverse reactions in > 1% of patients included ILD (1.3%), IRR (1.1%), and rash (1.1%). Three percent of patients discontinued amivantamab due to adverse reactions. The most frequent adverse reactions leading to treatment discontinuation were IRR (1,1%), ILD (0.5%), and nail toxicity. (0.5%)

Overall, the safety profile of amivantamab in NSCLC was considered manageable and no major safety concerns were raised.

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## E ASSESSMENT OF BENEFIT-RISK PROFILE

Patients with locally advanced or metastatic NSCLC have poor prognosis, with a 5-year survival rate of < 10%. EGFR Exon 20 insertion mutations have been identified as oncogenic drivers in NSCLC in approximately up to 12% of cases. There are no approved therapies for patients with EGFR Exon 20 insertion-mutated NSCLC, and therefore, in the first-line setting, standard chemotherapy remains the mainstay treatment option. For those whose disease has progressed following platinum-based chemotherapy, treatment alternatives are very limited. Most EGFR Exon 20 insertion driver mutations in NSCLC are insensitive to immunotherapy and to approved EGFR tyrosine kinase inhibitors (TKIs). The clinical evidence on EGFR mutated subsets from the pivotal trials of other drugs suggest that ORR in second-line patients with NSCLC EFGR Exon 20 insertion mutations on available treatment alternatives may likely be not more than 20%.

Amivantamab is a first-in-class, bispecific antibody directed against EGF and MET receptors. The efficacy of amivantamab as a second-line agent was evaluated in a Phase 1, first-in-human, single-arm study (CHRYSALIS) that included 114 adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, whose disease progressed on or after platinum-based chemotherapy. The ORR was 37% (95% CI: 28%, 46%) as evaluated by INV with a median DOR of 12.5 months (95% CI: 6.5, 16.1), which was considered clinically meaningful in the context of the target patient population in whom treatment options are limited. While the final analysis is still awaited, the overall evidence from the ORR and the duration of response is considered adequate to support the indication.

In terms of safety, amivantamab was generally well tolerated in the clinical studies and the safety profile is consistent with what is seen with other EGFR and MET inhibitors with which the clinicians are familiar in the clinical setting. The most common adverse reactions (≥ 20%) were rash, IRR, paronychia, fatigue, oedema, stomatitis, nausea, and constipation. Serious adverse reactions related to amivantamab were reported in 5% of the subjects, the most common of which included ILD, IRR, and rash. Three percent of patients discontinued amivantamab due to adverse reactions, and the most frequent were IRR, ILD, and nail toxicity. These risks have been adequately described in the local package insert with warnings and precautions, as well as dose adjustment recommendations in the event of toxicities.

Considering that advanced NSCLC is a life-threatening condition, the risks associated with the amivantamab therapy are considered acceptable, and thus, the benefits of amivantamab outweigh the risks in the treatment of subjects with locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy. The benefit-risk is considered favourable.

## F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Rybrevant for the treatment of patients with locally advanced or NSCLC with activating EGFR Exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy was deemed favourable and approval of the product registration was granted on 13 July 2022. The approval of this application is subject to the submission of the final study reports of the Phase 1 study (Study EDI1001) and the confirmatory Phase 3 study (Study 61186372NSC3001).

## APPROVED PACKAGE INSERT AT REGISTRATION

# PRODUCT NAME

RYBREVANT® (amivantamab) concentrate for solution for infusion

# DOSAGE FORMS AND STRENGTHS

Amivantamab is a fully-human immunoglobulin G1(IgG1)-based bispecific antibody directed against the epidermal growth factor (EGF) and mesenchymal-epidermal transition (MET) receptors, produced by a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology (see *Pharmacodynamic Properties - Mechanism of action*).

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

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

For excipients, see *List of Excipients*.

# CLINICAL INFORMATION

## Indications

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

## Dosage and Administration

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

Administer pre-infusion medications (see *Dosage and Administration – Pre-infusion medications*).

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

### Dosage – adults (≥18 years)

The recommended dose of RYBREVANT® is provided in Table 1, and the dosing schedule is provided in Table 2 (see *Infusion Rates – Table 4*).

**Table 1: Recommended Dose of RYBREVANT®**

| Body Weight of Patient (at Baseline*) | Recommended Dose | Number of 350 mg/7 mL RYBREVANT® Vials |
|---|---|---|
| Less than 80 kg | 1050 mg | 3 |
| Greater than or equal to 80 kg | 1400 mg | 4 |

* Dose adjustments not required for subsequent body weight changes.

**Table 2: Dosing Schedule for RYBREVANT®**

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

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

### *Pre-infusion medications*

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

**Table 3: Pre-Medications**

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

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

### *Infusion Rates*

Administer RYBREVANT® infusion intravenously according to the infusion rates in Table 4. Due to the frequency of IRRs at the first dose, infusion via a peripheral vein at Week 1 and Week 2 should be considered to minimize drug exposure in the event of an IRR; infusion via central line may be administered for subsequent weeks. It is recommended for the first dose to be diluted as close to administration as possible to allow for maximal flexibility in IRR management.

**Table 4: Infusion Rates for RYBREVANT® Administration**

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

* After Week 5, patients are dosed every 2 weeks.

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

## Missed dose(s)

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

## Dose modifications

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

**Table 5: RYBREVANT® Dose Reductions for Adverse Reactions**

| **Body Weight at Baseline** | **Initial Dose** | **1st Dose Reduction** | **2nd Dose Reduction** | **3rd Dose Modification** |
|---|---|---|---|---|
| Less than 80 kg | 1050 mg | 700 mg | 350 mg | Discontinue RYBREVANT® |
| Greater than or equal to 80 kg | 1400 mg | 1050 mg | 700 mg | |

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

**Table 6: RYBREVANT® Dosage Modifications for Adverse Reactions**

| **Adverse Reaction** | **Severity** | **Dose Modification** |
|---|---|---|
| **Infusion-Related Reactions (IRR)** (see *Warnings and Precautions*) | Grade 1 to 3 | • Interrupt infusion at the first sign of IRRs.<br>• Additional supportive medications (e.g., additional glucocorticoids, antihistamine, antipyretics and antiemetics) should be administered as clinically indicated.<br>• Upon resolution of symptoms, resume infusion at 50% of the previous rate.<br>• If there are no additional symptoms, the rate may be increased per the recommended infusion rate (see Table 4).<br>• Pre-medications should be administered prior to the next dose. |
| | Recurrent Grade 3 or Grade 4 | Permanently discontinue. |
| **Interstitial Lung Disease / Pneumonitis** *(see Warnings and Precautions)* | Suspected ILD/ pneumonitis | Withhold. |
| | Confirmed ILD/ pneumonitis | Permanently discontinue. |
| **Skin and Nail Reactions** *(see Warnings and Precautions)* | Grade 2 | • Supportive care should be initiated.<br>• If there is no improvement after 2 weeks, consider reducing the dose (see Table 5). |
| | Grade 3 | • Supportive care should be initiated.<br>• Withhold until the adverse reaction improves to ≤ Grade 2<br>Resume at reduced dose (see Table 5). |
| | Grade 4 (including severe bullous, blistering or exfoliating skin conditions) | Permanently discontinue. |
| **Other Adverse Reactions** *(see Adverse Reactions)* | Grade 3 | • Withhold until adverse reaction improves to ≤ Grade 1 or baseline.<br>• Resume at same dose if recovery occurs within 1 week.<br>• Resume at reduced dose (see Table 5) if recovery occurs after 1 week.<br>• Consider permanently discontinuing if recovery does not occur within 4 weeks. |
| | Grade 4 | • Withhold until adverse reaction improves to ≤ Grade 1 or baseline. |

| | | |
|---|---|---|
| | | • Resume at reduced dose (see Table 5) if recovery occurs within 4 weeks.<br>• Consider permanently discontinuing if recovery does not occur within 4 weeks. |

## Special populations

### *Pediatrics (17 years of age and younger)*

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

### *Elderly (65 years of age and older)*

Of the 380 patients treated with RYBREVANT® in EDI1001, 41% were 65 years of age or older, and 11% were 75 years of age or older. No overall differences in safety or effectiveness were observed between patients ≥ 65 years of age and patients < 65 years of age. No dosage adjustment is necessary (see *Pharmacokinetic Properties*).

### *Renal impairment*

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

### *Hepatic impairment*

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

## Administration

### *Preparation for administration*

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

1. Determine the dose required (either 1050 mg or 1400 mg) and number of RYBREVANT® vials needed based on patient's baseline weight (see *Dosage*). Each vial of RYBREVANT® contains 350 mg of amivantamab.
2. Check that the RYBREVANT® solution is colorless to pale yellow. Do not use if discoloration or visible particles are present.
3. Withdraw and then discard a volume of either 5% dextrose [glucose] solution or 0.9% sodium chloride solution from the 250 mL infusion bag equal to the volume of RYBREVANT® to be added (i.e., discard 7 mL diluent from the infusion bag for each RYBREVANT® vial). Infusion bags must be made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE), or polyolefin blend (PP+PE).

4. Withdraw 7 mL of RYBREVANT® from each vial and add it to the infusion bag. The final volume in the infusion bag should be 250 mL. Each vial contains a 0.5 mL overfill to ensure sufficient extractable volume. Discard any unused portion left in the vial.
5. Gently invert the bag to mix the solution. Do not shake.
6. Visually inspect the diluted solution before administration. Do not use if discoloration or visible particles are observed.
7. Diluted solutions should be administered within 10 hours (including infusion time) at room temperature (15°C to 25°C) and in room light.

### *Administration*

1. Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.2 micrometer). Administration sets must be made of either polyurethane (PU), polybutadiene (PBD), PVC, PP, or PE.
2. Do not infuse RYBREVANT® concomitantly in the same intravenous line with other agents.
3. This medicinal product is for single use only. Any unused medicinal product should be disposed of in accordance with local requirements.

## Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in *List of Excipients*.

## Warnings and Precautions

The data described in the WARNINGS AND PRECAUTIONS reflects the safety profile of 380 patients with locally advanced or metastatic NSCLC who received 1050 mg (for patients < 80 kg) or 1400 mg (for patients ≥ 80 kg) of RYBREVANT® monotherapy in Study EDI1001.

### Infusion-related reactions

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

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

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 *Dosage and Administration*).

### Interstitial lung disease

Interstitial lung disease (ILD) or ILD-like adverse reactions (e.g. pneumonitis) occurred in 2.6% of patients treated with RYBREVANT®. Patients with a medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD have not been studied.

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

### Skin and nail reactions

Rash (including dermatitis acneiform), pruritis and dry skin occurred in 76% of patients treated with RYBREVANT®. Most cases were Grade 1 or 2, with Grade 3 events occurring in 3% of patients. Rash leading to RYBREVANT® discontinuation occurred in 0.3% of patients. Rash usually developed within the first 4 weeks of therapy, with a median time to onset of 14 days. Nail toxicity occurred in patients treated with RYBREVANT®. Most events were Grade 1 or 2, with Grade 3 nail toxicity occurring in 1.8% of patients.

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

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

### Eye disorders

Eye disorders, including keratitis (0.5%), occurred in 9% of patients treated with RYBREVANT®. Other reported adverse reactions included dry eye, blurred vision, eye pruritus, visual impairment, aberrant eyelash growth, ocular hyperemia, conjunctival hyperemia, blepharitis and uveitis. All events were Grade 1-2. Refer patients presenting with worsening eye symptoms promptly to an ophthalmologist and advise discontinuation of contact lenses until symptoms are evaluated.

## Interactions

No drug interaction studies have been performed.

## Pregnancy, Breast-feeding and Fertility

### 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.

### Breast-feeding

It is not known whether RYBREVANT® is excreted in human or animal milk or affects milk production. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from amivantamab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. 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®.

### Contraception

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®. 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.

## Effects on Ability to Drive and Use Machines

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

## Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of amivantamab based on the comprehensive assessment of the available adverse event information. A causal relationship with amivantamab cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of

a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of RYBREVANT® was evaluated in Study EDI1001, which included 380 patients with locally advanced or metastatic NSCLC after failure of platinum-based chemotherapy. Patients received RYBREVANT® 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 4.1 months (range: 0.0 to 39.7 months).

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

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

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

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

| **System Organ Class**<br>Adverse Reaction | **Frequency (all grades)** | **All Grades (%)** | **Grade 3-4 (%)** |
|---|---|---|---|
| **Skin and subcutaneous tissue disorders** | | | |
| Rash [a] | Very common | 76 | 3 |
| Nail toxicity [b] | Very common | 47 | 2 |
| Dry skin [c] | Very common | 19 | 0 |
| Pruritus | Very common | 18 | 0 |
| Toxic epidermal necrolysis | Uncommon | 0.3 | 0.3 |
| **Injury, poisoning and procedural complications** | | | |
| Infusion-related reaction | Very common | 67 | 2 |
| **Gastrointestinal disorders** | | | |
| Stomatitis [d] | Very common | 24 | 0.5 |
| Nausea | Very common | 23 | 0.5 |
| Constipation | Very common | 23 | 0 |
| Vomiting | Very common | 12 | 0.5 |
| Diarrhea | Very common | 11 | 2 |
| Abdominal pain [e] | Common | 9 | 0.8 |
| **Metabolism and nutrition disorders** | | | |
| Hypoalbuminemia [f] | Very common | 31 | 2 |

| **System Organ Class**<br>Adverse Reaction | **Frequency (all grades)** | **All Grades (%)** | **Grade 3-4 (%)** |
|---|---|---|---|
| Decreased appetite | Very common | 16 | 0.5 |
| Hypocalcemia | Very common | 10 | 0.3 |
| Hypokalemia | Common | 9 | 2 |
| Hypomagnesemia | Common | 8 | 0 |
| **General disorders and administration site conditions** | | | |
| Edema [g] | Very common | 26 | 0.8 |
| Fatigue [h] | Very common | 26 | 0.8 |
| **Investigations** | | | |
| Alanine aminotransferase increased | Very common | 15 | 2 |
| Aspartate aminotransferase increased | Very common | 13 | 1 |
| Blood alkaline phosphatase increased | Very common | 12 | 0.5 |
| **Nervous system disorders** | | | |
| Dizziness [i] | Very common | 13 | 0.3 |
| **Musculoskeletal and connective tissue disorders** | | | |
| Myalgia | Very common | 11 | 0.3 |
| **Eye disorders** | | | |
| Other eye disorders [j] | Common | 6 | 0 |
| Visual impairment [k] | Common | 3 | 0 |
| Growth of eyelashes [l] | Common | 1 | 0 |
| Keratitis | Uncommon | 0.5 | 0 |
| Uveitis | Uncommon | 0.3 | 0 |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Interstitial lung disease [m] | Common | 3 | 0.5 |

[a] Rash: acne, dermatitis, dermatitis acneiform, erythema, erythema multiforme, folliculitis, impetigo, palmar-plantar erythrodysesthesia syndrome, perineal rash, perioral dermatitis, pustule, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin lesion

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

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

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

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

[f] Hypoalbuminaemia: blood albumin decreased, hypoalbuminemia

[g] Edema: eye edema, eyelid edema, face edema, generalized edema, localized edema, edema, edema peripheral, periorbital edema, peripheral swelling, swelling face

[h] Fatigue: asthenia, fatigue

[i] Dizziness: dizziness, dizziness exertional, vertigo

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

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

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

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

## Overdose

### Symptoms and signs

There is no information on overdosage with RYBREVANT®.

### Treatment

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

# PHARMACOLOGICAL PROPERTIES

## Pharmacodynamic Properties

Pharmacotherapeutic group: EGFR and MET inhibitor, ATC code: L01FX18

### Mechanism of action

Amivantamab is a low-fucose, fully-human IgG1-based EGFR-MET bispecific antibody with immune cell-directing activity that targets tumors with activating and resistance EGFR mutations and MET mutations and amplifications. Amivantamab binds to the extracellular domains of EGFR and MET.

Preclinical studies show amivantamab is active against tumors with primary EGFR activating mutations such as Exon 19 deletions, L858R substitution, and Exon 20 insertion mutations; secondary EGFR resistance mutations such as T790M and C797S; and resistance to EGFR inhibition due to activation of the MET pathway. Amivantamab disrupts EGFR and MET signaling functions through blocking ligand binding and enhancing degradation of EGFR and MET, thereby preventing tumor growth and progression. 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.

### Pharmacodynamic effects

#### *Albumin*

Amivantamab decreased serum albumin concentration, a pharmacodynamic effect of MET inhibition, typically during the first 8 weeks; thereafter, albumin concentration stabilized for the remainder of amivantamab treatment.

#### *Immunogenicity*

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

## Clinical studies

### *Locally advanced or metastatic NSCLC with exon 20 insertion mutations*

EDI1001 (CHRYSALIS) is a multicenter, open-label, multi-cohort study conducted to assess the safety and efficacy of RYBREVANT® in subjects with locally advanced or metastatic NSCLC. Efficacy was evaluated in 114 subjects with locally advanced or metastatic NSCLC who had EGFR Exon 20 insertion mutations as determined by previous local standard of care testing, whose disease had progressed on or after platinum-based chemotherapy, and who had median follow-up of 12.5 months. RYBREVANT® was administered intravenously at 1050 mg for subjects < 80 kg or 1400 mg for subjects ≥ 80 kg once weekly for 4 weeks, then every 2 weeks starting at Week 5 until disease progression or unacceptable toxicity.

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

Efficacy results are summarized in Table 8.

**Table 8: Efficacy Results for EDI1001 (CHRYSALIS)**

| | **BICR Assessment (N=114)** | **Investigator Assessment (N=114)** |
|---|---|---|
| **Overall Response Rate**[a,b] (95% CI) | 43% (34%, 53%) | 37% (28%, 46%) |
| Complete response | 3% | 0% |
| Partial response | 40% | 37% |
| **Clinical Benefit Rate**[a,c] (95% CI) | 74% (65%, 82%) | 75% (67%, 83%) |
| **Duration of Response**[a] **(DOR)** | | |
| Median (95% CI), months[d] | 10.8 (6.9, 15.0) | 12.5 (6.5, 16.1) |
| Patients with DOR ≥ 6 months | 55% | 64% |
| **Median Progression-Free Survival**[a] (95% CI), months | 6.7 (5.5, 9.7) | 6.9 (5.6, 8.6) |
| **Median Time to Treatment Failure** (95% CI), months | 8.1 (6.7, 10.6) | |
| **Median Overall Survival** (95% CI), months | 22.8 (17.5, NE) | |

BICR=Blinded Independent Central Review; NE=Not Estimable

[a] by RECIST v1.1
[b] Confirmed response.
[c] Clinical benefit rate is defined as complete response + partial response + stable disease (duration of at least 11 weeks).
[d] Based on Kaplan-Meier estimate

Anti-tumor activity was observed across studied mutation subtypes.

## Pharmacokinetic Properties

Amivantamab area under the concentration-time curve ($AUC_{1week}$) increases proportionally over a dose range from 350 to 1750 mg (0.33 to 1.67 times the recommended dose for subjects < 80 kg and 0.25 to 1.25 times the recommended dose for subjects ≥ 80 kg).

Following administration of RYBREVANT® at the recommended dose and schedule, the mean ± SD serum maximal concentration ($C_{max}$) was 836 ± 264 mcg/mL at 1050 mg for subjects < 80 kg and 655 ± 109 mcg/mL at 1400 mg for subjects ≥ 80 kg at the end of weekly dosing following the fifth dose. The mean ± SD $AUC_{1week}$ following the fifth dose was 94,946 ± 35,440 mcg.h/mL at 1050 mg for subjects < 80 kg and 76,946 ± 14,557 mcg.h/mL at 1400 mg for subjects ≥80 kg. The mean serum $AUC_{1week}$ was approximately 2.9-fold higher after the fifth dose following the weekly dosing compared to the first dose.

When RYBREVANT® was administered, amivantamab steady state was achieved approximately 2 months into the every 2-week dosing period (by the ninth infusion) at 1050 mg, and amivantamab mean ± SD ratio of $AUC_{1week}$ at steady state to $AUC_{1week}$ after the first dose was 2.44 ± 0.54.

### Distribution

Amavintamab mean ± SD volume of distribution estimated from population PK parameters was 5.13 ± 1.78 L following administration of the recommended dose of RYBREVANT®.

### Elimination

Amivantamab clearance decreased with increasing dose and with multiple dosing. The mean ± SD linear clearance was estimated to be 360 ± 144 mL/day and the mean ± SD estimated terminal half-life associated with linear clearance estimated from population PK parameter estimates was 11.3 ± 4.53 days following administration of the recommended dose of RYBREVANT®.

### Special populations

#### *Pediatrics (17 years of age and younger)*

The pharmacokinetics of RYBREVANT® in pediatric patients have not been investigated.

#### *Elderly (65 years of age and older)*

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

### *Renal impairment*

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

### *Hepatic impairment*

Changes in hepatic function are unlikely to have any effect on the elimination of amivantamab since IgG1-based molecules such as amivantamab are not metabolized through hepatic pathways.

No clinically meaningful effect in the pharmacokinetics of amivantamab was observed based on mild hepatic impairment [(total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5 x ULN)]. The effect of moderate (total bilirubin 1.5 to 3 times ULN) and severe (total bilirubin > 3 times ULN) hepatic impairment on amivantamab pharmacokinetics is unknown.

### *Gender*

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

### *Weight*

The central volume of distribution and clearance of amivantamab increased with increasing body weight. Similar amivantamab exposures were achieved at the recommended dose of RYBREVANT® in patients with a body weight < 80 kg who received 1050 mg and patients with a body weight ≥ 80 kg who received 1400 mg.

## NON-CLINICAL INFORMATION

In repeat-dose toxicity studies in cynomolgus monkeys, amivantamab was well-tolerated at weekly doses up to 120 mg/kg intravenously for 6 weeks or 3 months (~6-8x $C_{max}$ and ~5-7x AUC human exposure for 1050 and 1400 mg intravenous doses). There were no effects on cardiovascular, respiratory, and nervous system function. Clinical pathology demonstrated non-adverse elevations in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and globulins, and non-adverse decreases in albumin when compared to the control group. All these values returned to normal ranges in recovery groups. A subcutaneous local tolerance study showed that amivantamab was well tolerated at injection sites in cynomolgus monkeys administered two 125 mg/kg weekly doses.

## Carcinogenicity and Mutagenicity

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

## Reproductive Toxicology

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

# PHARMACEUTICAL INFORMATION

## List of Excipients

EDTA disodium salt dihydrate

L-Histidine

L-Histidine hydrochloride monohydrate

L-Methionine

Polysorbate 80

Sucrose

Water for Injection

## Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in *Dosage and Administration*.

## Shelf Life

Unopened vials:
See expiry date on the outer pack.

After dilution:
Since amivantamab solutions do not contain a preservative, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used immediately. Administer diluted solutions within 10 hours (including infusion time) at room temperature (15°C to 25°C) and in room light.

## Storage Conditions

Store in a refrigerator at 2°C to 8°C.

Do not freeze.

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

For storage conditions after dilution of the medicinal product, see Shelf-Life.

Keep out of the sight and reach of children.

## Nature and Contents of Container

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

## Instructions for Use and Handling and Disposal

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

## BATCH RELEASER

Cilag AG
Hochstrasse 201
8200 Schaffhausen
Switzerland

## PRODUCT REGISTRANT

Johnson & Johnson Pte Ltd
2 Science Park Drive
#07-13, Ascent
Singapore Science Park 1
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