Date: 29 March 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Rybrevant

International non-proprietary name: amivantamab

Pharmaceutical form: concentrate for solution for infusion

Dosage strength: 350 mg/7 ml

Route(s) of administration: intravenous

Marketing Authorisation Holder: Janssen-Cilag AG

Marketing Authorisation No.: 68380

Decision and Decision date: approved (temporary authorisation in accordance with Art. 9a TPA) on 20 January 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of the SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
ADME	Absorption, Distribution, Metabolism, Elimination
Akt	Protein kinase B, serine/threonine protein kinase family
ALT	Alanine aminotransferase
AMIV	Amivantamab
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
BIRC	Blinded independent review committee
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DOR	Duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	Epidermal growth factor receptor
ERA	Environmental Risk Assessment
ERK	Extracellular-signal Regulated Kinase
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
ins	Insertion mutations
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MET	Mesenchymal-epithelial transition factor receptor / hepatocyte growth factor receptor
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RECIST	Response evaluation criteria in solid tumours
RMP	Risk Management Plan
SAE	Serious adverse events
SwissPAR	Swiss Public Assessment Report
TKIs	Tyrosine kinase inhibitors
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020 on Medicinal Products and Medical Devices (SR 812.21)
TEAE	Treatment-emergent adverse events
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
TRAE	Treatment-related adverse events

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance amivantamab of the medicinal product mentioned above.

Fast-track authorisation procedure (FTP)
The applicant requested a fast-track authorisation procedure in accordance with Article 7 of the TPO.

Temporary authorisation for human medical products
The applicant requested a temporary authorisation in accordance with Art. 9a TPA.

2.2 Indication and Dosage

2.2.1 Requested Indication

Rybrevant is indicated as monotherapy for the treatment of patients with metastatic or unresectable 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-containing chemotherapy.

2.2.2 Approved Indication

Rybrevant is indicated as monotherapy for the treatment of patients with metastatic or unresectable, non-small cell lung cancer (NSCLC) with activating insertion mutations in Exon 20 of the epidermal-growth factor receptor (EGFR) gene whose disease has progressed on or after platinum-containing chemotherapy.

2.2.3 Requested Dosage

The proposed dose is 1050 mg for patients <80 kg body weight (at baseline) or 1400 mg for patients ≥80 kg body weight (at baseline), administered as an intravenous (IV) infusion once weekly for 4 weeks, then every 2 weeks thereafter until disease progression or unacceptable toxicity. The first cycle 1 dose is split over 2 days with the first infusion of 350 mg on day 1 and 700 mg (body weight <80 kg) or 1050 mg (body weight ≥80 kg) on day 2.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	11 May 2021
Formal control completed	14 May 2021
List of Questions (LoQ)	15 July 2021
Answers to LoQ	4 October 2021
Predecision	18 November 2021
Answers to Predecision	3 January 2022
Final Decision	20 January 2022
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

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3 Medical Context

Treatment of lung cancer patients depends on the histology, molecular characteristics, tumour stage and an assessment of the patient's overall medical condition. An improved understanding of the molecular pathways that drives malignancy in non-small cell lung cancer (NSCLC) has led to the development of agents that target specific molecular pathways in malignant cells. Therapy can then be individualised based on the specific abnormality if present in a given NSCLC patient. Among these patients, the most frequent targetable abnormalities are activating epidermal growth factor receptor (EGFR) gene mutations, which are identified in approx. 10-15% of adenocarcinomas in western populations[1]. EGFR driver mutations in other histological subtypes are rather rare.

The most frequently identified EGFR mutations are Exon 19del and L858R, which are identified in 80-85% of subjects with activating EGFR mutations[2], and are effectively targeted by multiple approved EGFR tyrosine kinase inhibitors (TKIs).

Although NSCLC patients with insertion mutations (ins) in EGFR Exon 20 are believed to share a similar biology with other EGFR mutated NSCLC[3], the protein structure associated with this group of EGFR mutations hinders access to the receptor active site for some EGFR TKIs. Thus, EGFR Exon20ins are associated with *de novo* resistance to most approved EGFR inhibitors and correlate with a poor patient prognosis. Compounds with the ability to effectively target EGFR Exon20ins present an unmet medical need.

Amivantamab (AMIV) is a fully-human IgG1-based EGFR-MET bispecific antibody that targets tumours with activating EGFR mutations. AMIV binds to the extracellular domains of EGFR and MET (mesenchymal-epithelial transition factor receptor). AMIV inhibits the EGFR and MET signalling pathways, thereby preventing tumour growth and progression.

4 Quality Aspects

4.1 Drug Substance

Amivantamab, the active substance of Rybrevant is a humanised, bispecific, low fucose recombinant monoclonal antibody (IgG1) that specifically binds to the extracellular domains of EGFR and MET.
In tumour models, amivantamab was able to disrupt EGFR and MET signalling functions by blocking ligand binding and increasing degradation of EGFR and MET. In addition, specific binding of amivantamab on the surface of tumour cells allows for targeting of these cells for destruction by immune effector cells through antibody-dependent cellular cytotoxicity (ADCC) and trogocytosis (mechanism of action).
Amivantamab is a heterodimer, consisting of two different heavy chains and two different light chains, joined by disulfide bonds. The major glycoform has a molecular mass of 148,209 Da. Amavantamab is prepared by controlled reduction and oxidation of the parental homodimer monoclonal antibodies, anti-EGFR and anti-cMET. For preferential formation of the heterodimer, two amino acid substitutions in the CH3 domains (K411R, F413L) were introduced into the Fab arms of the parental antibodies. Amivantamab carries N-Glycan moieties in the Fc region at EGFR heavy chain Asn305 and cMET heavy chain Asn299. Both parental monoclonal antibodies, anti-EGFR and anti-cMET, are produced by mammalian cells derived from Chinese hamster ovary using recombinant DNA technology. For enhancement of ADCC activity, low-fucose cell lines were used.

[1] J Remon et al, 2020 EGFR exon 20 insertions in advanced non-small cell lung cancer: A new history begins. Cancer Treat Rev. 2020 Nov;90:102105.
[2] ME Arcila et al. EGFR exon 20 insertion mutations in lung adenocarcinomas: prevalence, molecular heterogeneity, and clinicopathologic characteristics, Mol Cancer Ther. 2013 Feb;12(2):220-9.
[3] F Wang et al. EGFR exon 20 insertion mutations in non-small cell lung cancer, Translational Cancer Research, Vol 9, No 4, April 2020

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The generation and characterisation of the host cell lines and the establishment of the cell banks used for production of amivantamab are described in sufficient detail.
Suspension cells and serum-free media are used during the cell culture process. Amivantamab is secreted into the culture medium and separated from cell debris by centrifugation and filtration steps. The purification process comprises several chromatographic and filtration steps as well as virus inactivation and virus retention filtration. Commercial-scale process validation batches were manufactured to demonstrate consistent performance, reproducibility and robustness of the manufacturing process according to a process validation master plan.
The changes in manufacturing process of the drug substance during development are supported by process and analytical comparability studies which were performed in accordance with regulatory guidelines.
Extensive characterisation of the physicochemical and biological properties of amivantamab was performed using state-of-the-art techniques. Product and process-related substances and impurities are adequately addressed.
The active substance batch release procedures comprise a panel of tests to assure identity, potency and purity of amivantamab and to control impurities within acceptable limits. The non-compendial test procedures are validated according to ICH guidelines.
The proposed storage conditions and shelf life of the drug substance in its commercial container are justified by the presented stability data.

4.2 Drug Product

The amivantamab final drug product is supplied as a sterile 50 mg/mL liquid concentrated solution for infusion in a vial. Each vial contains 350 mg of amivantamab in a 7.0 mL nominal fill volume. The primary packaging consists of a 8 mL Type 1 glass vial with an elastomeric closure and an aluminium seal with a flip-off cap. The drug product is formulated in a histidine buffered aqueous solution, containing sucrose, L-methionine, EDTA (ethylenediaminetetraacetic acid) and polysorbate 80. All excipients are of compendial grade. For intravenous administration, the drug product is to be diluted in 5% dextrose or 0.9% sodium chloride intravenous solution. Compatibility with diluents and prescribed infusion sets including in-line filters is demonstrated. Upon dilution, the solution for infusion is physico-chemically stable at 15 - 25°C for up to 10 hours.
The manufacturing process of the finished drug product consists of thawing, pooling, sterile filtration, aseptic filling/stoppering/sealing, inspection, labelling and secondary packaging. Process validation studies were conducted at commercial scale using four consecutive validation batches.
The specifications include appropriate tests for appearance, identity, endotoxin, sterility, potency, total protein content and purity. The acceptance limits are justified based on compendial requirements, experience from clinical trials, statistical analysis and risk assessment. Analytical procedures are validated in accordance with ICH guidelines. Batch analysis data of batches used in clinical studies as well as commercial-scale batches from the current manufacturing site were provided and indicate a consistent manufacturing process.
The claimed shelf life of 24 months for drug product stored at 2 – 8°C is justified based on stability studies in accordance with ICH.
The manufacturing process of the drug substance and drug product includes adequate control measures to prevent contamination and maintain control with regard to safety from adventitious agents.

4.3 Quality Conclusions

Satisfactory and consistent quality of the drug substance and drug product have been demonstrated.

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5 Nonclinical Aspects

For the nonclinical testing strategy, the applicant considered the recommendations outlined in ICH S6(R1) and S9.

Pharmacodynamics

The sequence homology between the extracellular domains of human EGFR and MET is ≥99% for cynomolgus monkeys and 88% for rodents.
Amivantamab bound human EGFR and MET with K_D 1.43 nM and 0.04 nM. Binding to the extracellular domains of human and cynomolgus monkey receptors was similar (EC_{50} 0.37- 0.57 nM). MET phosphorylation induced by amivantamab was similar in human and monkey cells (EC_{50} 0.15 - 0.22 nM). Amivantamab bound cell-expressed EGFR in cynomolgus cells only weakly while binding to EGFR on human cells was similar to recombinant EGFR (EC_{50} 0.1 to 2.2 nM).
Amivantamab inhibited ligand binding, ligand-mediated receptor phosphorylation and downstream signalling (Akt and ERK phosphorylation), ligand-induced receptor internalisation, cellular proliferation, and EGFR homo- and EGFR/Erb2 heterodimerisation in the lower nanomolar range. Potency was in general higher for wildtype receptors than in cell lines with MET amplifications or multiple mutations. Combination with tyrosine kinase inhibitors (TKIs) partially showed a synergistic effect, mainly in cell lines with primary EGFR mutations.
Efficacy, i.e. tumour growth inhibition and/or downmodulation of receptor phosphorylation, was shown in various murine lung tumour models with wildtype EGFR, primary activating EGFR mutations, resistant EGFR mutations, hepatocyte growth factor (HGF) overexpression or *MET* gene amplification. In genetically engineered mice carrying an EGFR-Exon19 deletion or an additional resistant mutation (T790M), amivantamab had only moderate anti-tumour activity in contrast to first or second generation TKIs. In xenograft models with EGFR exon 20 insertion mutations, amivantamab inhibited tumour growth similarly to a comparator anti-EGFR antibody and usually more efficiently than TKIs. There was no activity against P772-H773insDNP and H773-V774insNPH mutations.
In vitro and *in vivo* studies showed that tumour cell inhibition was dependent on Fc-mediated effector function with involvement of natural killer (NK) cells, monocytes and macrophages, supporting a contribution of antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis (ADCP). Trogocytosis possibly contributed to receptor downregulation. The kinetics of binding to human and cynomolgus FcγRI were similar with K_D ≤7.8 nM.
Cross-reactivity studies demonstrated comparable binding in human and cynomolgus monkey tissues.
Safety pharmacology endpoints for the cardiovascular, respiratory and central nervous systems were included in the toxicology studies and did not raise concerns.

Pharmakokinetics

Bioanalytical methods were validated for the quantification of amivantamab and anti-drug antibody (ADA). PK studies with intravenous administration in cynomolgus monkeys indicated target-mediated drug disposition. Toxicokinetics showed no gender differences, an increase in $t_{1/2}$ to 10 days after repeated dosing, accumulation ≤ 2.4-fold and a roughly dose-proportional increase in AUC in the higher dose range.
Conventional studies on distribution, metabolism, excretion and PK-drug interactions were not conducted, which is acceptable for an IgG1 antibody and in accordance with ICH S6 recommendations.

Toxicology

The cynomolgus monkey was selected as the toxicology species, which is acceptable as it is a pharmacologically relevant species. Activity on EGFR is probably slightly underestimated compared to humans but pharmacological activity on both EGFR and MET was demonstrated. The dosing route (IV, slow bolus) and dosing scheme (weekly) are appropriate to support the maintenance dosing in humans every two weeks.

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One-month tolerability (up to 100 mg/kg) and 6-week and 3-month (both up to 120 mg/kg) toxicology studies included an assessment of acute toxicity and are considered adequate for an ICH S9 indication.
Amivantamab was well tolerated up to the highest doses, which were associated with exposures at least 5.5-fold the mean clinical exposures for both treatment regimens (1050 mg < 80 kg body weight and 1400 mg ≥ 80 kg body weight). Amivantamab-related findings were observed in the skin, kidney, liver and haematological system. The findings are consistent with the known class effects and were reversible. This is considered acceptable for an ICH S9 indication.

Genotoxicity and carcinogenicity studies were not conducted with amivantamab in line with ICH recommendations.
A weight-of-evidence assessment was provided to waive reproductive toxicity studies based on the known detrimental effects of EGFR and MET inhibition for embryofoetal development, which is acceptable and adequately mentioned in the information for healthcare professionals.
In vitro assessments of cytokine release, serum compatibility and haemolytic activity did not raise concerns.

There are no concerns with regard to the excipients and impurities.

Although major toxicities were not identified in the toxicological studies, known class effects were included in the RMP and in the information for healthcare professionals.

Nonclinical Conclusions
The pharmacological and toxicological properties of amivantamab, a bispecific antibody against EGFR and MET, were sufficiently characterised in the nonclinical studies. All safety-relevant nonclinical data are mentioned in the information for healthcare professionals. The submitted nonclinical documentation is considered sufficient to support the approval of Rybrevant in the requested indication.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

The evaluation of the clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by the FDA. The available assessment report and respective product information from the FDA were used as a basis for the clinical pharmacology evaluation.
For further details concerning clinical pharmacology, see section 8.1 of this report.

6.2 Dose Finding and Dose Recommendation

The dose finding of amivantamab (AMIV) monotherapy was based on the clinical data from the dose escalation part of the 61186372EDI1001 (CHRYSALIS) study that included NSCLC patients with disease progression after prior therapy with the standard of care. The study tested a flat-dose of intravenous AMIV once weekly for the first 4 weeks followed by subsequent AMIV application every two weeks. Due to frequent infusion-related reactions, the first drug administration was later split over days 1 and 2 (for cycle 1 only). EGFR inhibition-mediated rash was first observed in the 350 mg AMIV cohort. First treatment response was observed in the 700 mg dose cohort. Based on the pharmacokinetic and pharmacodynamic analyses, the applicant determined that the drug exposure was similar between patients with a body weight of <80 kg treated with a 1050 mg flat-dose compared to patients with a body weight of ≥80 kg treated with 1400 mg. Additional analyses showed that this 1050/1400 mg dose demonstrated a higher coverage of the target efficacious concentration compared to lower doses. The applicant determined the recommended phase 2 dose to be 1050 mg for patients with <80 kg body weight and 1400 mg for patients with ≥80 kg body weight (later abbreviated as 1050/1400 mg dose).

6.3 Efficacy

Data from one non-randomised study were submitted to support the efficacy and safety of AMIV:

Study 61186372EDI1001 (CHRYSALIS)
To support the efficacy of AMIV, the applicant submitted data from the non-randomised, first-in-human study 61186372EDI1001 (CHRYSALIS) in patients with advanced NSCLC. The study consisted of two parts: a dose escalation and a dose expansion part. The dose expansion cohort consisted of multiple cohorts that tested AMIV within molecularly defined tumour subgroups. To support the requested indication, the applicant submitted the study data that concerned NSCLC patients with EGFR Exon20ins who were treated with AMIV monotherapy. The primary efficacy population was based on pooled efficacy analyses of NSCLC patients with EGFR Exon20ins after platinum-based chemotherapy treated with AMIV 1050/1400 mg dose from different study cohorts.

The relevant efficacy population included adult patients with metastatic or unresectable NSCLC after prior platinum-based chemotherapy or who were ineligible for or had refused all other currently available therapeutic options. Patients were required to have a documented EGFR Exon20ins mutation, Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0-1 as well as adequate organ (hepatic, renal, bone marrow) function. The study excluded patients with continuous oxygen therapy, history of interstitial lung disease, untreated active brain metastases (patients with previously treated stable brain metastases were allowed), clinically significant cardiovascular disease, relevant ongoing infection or a planned invasive operative procedure.

In the dose expansion part, patients received the 1050/1400 mg dose of AMIV. Treatment was administered until disease progression, unacceptable toxicity or withdrawal of consent. After the discontinuation of study treatment, patients were followed up for survival until the end of the study. Disease assessment was performed every 6 weeks with CT or MRI until disease progression; post-baseline CNS imaging was performed when clinically indicated. Tumour response was evaluated

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according to response evaluation criteria in solid tumours (RECIST) 1.1 as determined by the investigator and blinded independent review committee (BIRC).

The primary efficacy endpoint was the overall response rate (ORR). Other relevant efficacy endpoints were progression-free survival (PFS), overall survival (OS) and duration of response (DOR).

The most recent provided data cut-off was from March 2021.

The median age of all study patients with NSCLC Exon20ins after platinum-based chemotherapy treated with 1050/1400 mg dose was 62 years. Sixty-one percent were females, 52% were Asian, 37% were Caucasian, 29% had an ECOG PS of 0, 70% an ECOG PS of 1, 43% had a history of smoking, 79% had initial stage IV disease, 54% had lymph node metastases, 44% had bone metastases, 25% had brain metastases and 11% had liver metastases.

The primary efficacy population consisted of 81 patients with NSCLC EGFR Exon20ins after platinum-based chemotherapy who were evaluable for efficacy and received the 1050/1400 mg AMIV dose on or before 5 February 2020. In the primary efficacy population, the median number of prior systemic treatments was n=2, all patients had received prior platinum-based chemotherapy, 46% had had prior immunotherapy and 21% had had prior EGFR TKIs. In this population, the most common Exon20ins mutations were A767 (23.5%), S768 (16.0%), D770 (11.0%) and N771 (11.0%).

At the most recent data cut-off, the median follow-up period was 14.5 months and the median duration of study treatment was 5 months. The ORR according to the investigator was 38% [CI95% 28%, 50%]. The ORR according to the BIRC was 43% [CI95% 32%-55%]. The median PFS according to both investigator and BIRC assessments was 8.3 months. The median DOR according to the investigator was 12.5 months. The median DOR according to the BIRC was 11.04 months. The median OS was 22.77 months.

The applicant also provided supportive efficacy data on patients with NSCLC EGFR Exon20ins after platinum-based chemotherapy who received the first AMIV dose on or before 4 June 2020 (n=114, larger patient population with a shorter median follow-up period) as well as NSCLC Exon20ins patients without prior chemotherapy (n=28) and patients who received a non-1050/1400 mg dose of AMIV (n=42). The efficacy results from these supportive populations were consistent with the reported findings of the primary efficacy population.

Relevant ongoing studies
The phase III study 61186372NSC3001 (PAPILLON) is testing AMIV in combination with carboplatin doublet versus carboplatin doublet alone in previously untreated locally advanced or metastatic NSCLC patients with EGFR Exon20ins.

6.4 Safety

The submitted AMIV safety database consisted of 489 patients treated with the 1050/1400 mg AMIV dose and included patients with NSCLC EGFR Exon20ins with prior chemotherapy and NSCLC patients without EGFR Exon20ins. The most recent safety data were provided with the March 2021 data cut-off. The median duration of treatment for patients in the safety database was 4.14 months.

Most patients in the submitted pooled safety analysis experienced at least one treatment-related adverse event (TRAE) of any grade (96%). The reported frequency of grade ≥3 treatment-emergent adverse events (TEAEs) was 41%. The rate of serious adverse events (SAEs) was 29% and for treatment-related SAEs, the reported rate was 6%. The frequency of TEAEs leading to death was 5%.

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The most frequent TEAEs of any grade were infusion-related reactions, paronychia, rash, dermatitis acneiform, hypoalbuminaemia, nausea, constipation, peripheral oedema, stomatitis and fatigue.

The most frequent grade ≥3 TEAEs were pneumonia, dyspnoea, pulmonary embolism, hyponatraemia, hypoalbuminaemia, hypokalaemia, infusion-related reactions, transaminase increase, hypophosphataemia, paronychia, diarrhoea, hypoxia, pleural effusion, hypotension and neutropenia.

The most frequent TRAEs of any grade were infusion-related reactions, paronychia, rash, dermatitis acneiform, hypoalbuminaemia, stomatitis, pruritus, dry skin, nausea, peripheral oedema, fatigue and transaminase increase.

In all AMIV-treated NSCLC patients (n=489), the following TEAEs leading to death were reported: pneumonia (n=6), respiratory failure (n=5) and dyspnoea (n=2), followed by sepsis, pulmonary sepsis, atypical pneumonia, adenovirus infection, acute respiratory failure, chronic respiratory failure, aspiration, aspiration pneumonia, cardio-respiratory distress, cardiac arrest and sudden death (n=1 each).

The most frequent SAEs according to System Organ Class were respiratory, thoracic or mediastinal disorders such as dyspnoea, pulmonary embolism and pneumonitis. These were followed by infections (in particular pneumonia), musculoskeletal disorders (mostly back pain), cardiac disorders (such as pericardial effusion) and injury or procedural complications (mostly infusion-related reactions).

Adverse events of special interest were infusion-related reactions, rash, paronychia, eye disorders, pneumonitis, hypoalbuminaemia and toxic epidermal necrolysis

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Treatment of NSCLC depends on the histology, molecular characteristics, tumour stage and an assessment of the patient's overall medical condition. An improved understanding of the molecular pathways that drive malignancy for this disease has led to the development of agents that target specific molecular pathways in malignant cells. The most frequently identified EGFR mutations are Exon 19del and L858R, which are effectively targeted by multiple approved EGFR TKIs. These agents demonstrated improved treatment outcomes for patients with EGFR TKI-sensitive disease. However, NSCLC arising from EGFR Exon20ins has to be distinguished due to the *de novo* resistance to most approved EGFR TKIs. There is a medical need to improve the outcomes of NSCLC patients with EGFR Exon20ins with disease progression on or after the standard platinum based chemotherapy.

The pivotal efficacy data were from the non-randomised study 61186372EDI1001 (CHRYSALIS). In the pooled primary efficacy population of NSCLC patients with Exon20ins after platinum-based chemotherapy, the reported ORR was 43%, the median DOR was 11.04 months, the median PFS was 8.3 months by BIRC assessment and the median OS was clinically relevant with 22.77 months.

The main deficiency of the submitted dossier is the lack of randomised clinical data to support the efficacy of amivantamab compared to the standard of care. However, results from the ongoing randomised phase III study 61186372NSC3001 (PAPILLON), which tests AMIV combined with platinum doublet versus platinum doublet alone, will provide potentially confirmatory evidence for the current indication.

Relevant reported toxicities for AMIV were rash, paronychia, eye disorders, pneumonitis, hypoalbuminaemia, peripheral oedema and infusion-related reactions. These adverse drug reactions were manageable and are adequately described in the product information. However, due to the

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design of study 61186372EDI1001 (CHRYSALIS), a direct comparison of safety to other agents was not possible.

Conclusion:
The reported efficacy benefit for AMIV for patients with metastatic and/or unresectable NSCLC EGFR Exon20ins after platinum-based chemotherapy is clinically meaningful and the safety profile appears to be manageable. The benefit-risk ratio is positive for temporary marketing authorisation. The clinical results from an ongoing phase III study 61186372NSC3001 (PAPILLON) will provide the required potentially confirmatory evidence to support the conversion of temporary marketing authorisation into an ordinary marketing authorisation.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Rybrevant was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

RYBREVANT has been authorized temporarily, see section "Properties/Effects".

RYBREVANT, concentrate for solution for infusion

Composition

Active substances

Amivantamab

Excipients

EDTA disodium salt dihydrate (corresponds to 17 µg sodium), L-Histidine, L-Histidine hydrochloride monohydrate, L-Methionine, Polysorbate 80, Sucrose (595 mg), Water for Injection.

Pharmaceutical form and active substance quantity per unit

RYBREVANT is available as a colorless to pale yellow concentrate for solution for infusion.
Each single-use vial contains 350 mg of amivantamab per 7 mL (50 mg of amivantamab per mL).

Indications/Uses

RYBREVANT is indicated as monotherapy for the treatment of patients with metastatic or unresectable, non-small cell lung cancer (NSCLC) with activating insertion mutations in Exon 20 of the epidermal-growth factor receptor (EGFR) gene whose disease has progressed on or after platinum-containing chemotherapy.

Dosage/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 / Administration” – Pre-infusion Medications).
If EGFR Exon 20 insertion mutation is detected using a validated plasma or tissue-based test, the patient is suitable for treatment with RYBREVANT (see “Pharmacodynamics - Clinical efficacy”).
It is recommended that patients are treated with RYBREVANT until disease progression or unacceptable toxicity.
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Usual dosage - Adults (≥18 years)

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

Table 1: Recommended Dose of RYBREVANT

Body Weight of Patient (at Baseline*)	Recommended Dose
Less than 80 kg	1050 mg
Greater than or equal to 80 kg	1400 mg

* 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

Infusion Rates

Administer RYBREVANT infusion intravenously according to the infusion rates in Table 3. 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 3: 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 4, 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.

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 (see table 4). As of week 2, administer antihistamines and antipyretics (see table 4). Administer antiemetics as needed.

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*	Paracetamol/Acetaminophen (650 to 1000 mg)	IV	15 to 30 minutes
		Oral	30 to 60 minutes
Glucocorticoid‡	Dexamethasone (10 mg) or Methylprednisolone (40 mg) or equivalent	IV	45 to 60 minutes

* Required at all doses.

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

Management of Infusion-Related Reactions

- Interrupt infusion at the first sign of IRRs (see Warnings and Precautions). Administer additional supportive medications (e.g., additional glucocorticoids, antihistamine, antipyretics, and antiemetics) as clinically indicated.
- Grade 1-3 (mild-severe): Upon recovery of symptoms, resume infusion at 50% of the previous rate. If there are no additional symptoms, the rate may be increased per the recommended infusion rate (see Table 3). Administer pre-infusion medications at next dose (see Table 4).
- Recurrent Grade 3 or Grade 4 (life-threatening): Permanently discontinue RYBREVANT (see "Warnings and Precautions").

Dose adjustment following undesirable effects

Interrupt RYBREVANT for Grade 3 or 4 adverse reactions until the adverse reaction resolves*. If an interruption is 7 days or less, restart RYBREVANT at current dose. If an interruption is longer than 7 days, consider restarting RYBREVANT at a reduced dose as outlined in Table 5. Permanently discontinue if recovery does not occur within 4 weeks.

Table 5: RYBREVANT Dose Modifications for Adverse Reactions

Body Weight at Baseline	Initial Dose	1st Dose Modification	2nd Dose Modification	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	

* Resolution is defined as ≤ Grade 1 non-hematologic toxicity or returning to baseline.

Skin and Nail Reactions

If the patient develops Grade 3 or poorly-tolerated Grade 2 skin or nail reactions, consider interrupting RYBREVANT until the adverse reaction improves (See "Warnings and Precautions"). Permanently discontinue RYBREVANT in case of Grade 4 skin AEs and severe bullous, blistering or exfoliating skin conditions (including toxic epidermal necrolysis (TEN)).

Interstitial Lung Disease

If the patient develops interstitial lung disease (ILD) or pneumonitis, permanently discontinue RYBREVANT (See "Warnings and Precautions").

Special dosage instructions

Patients with hepatic disorders

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 "Pharmacokinetics").

Patients with renal disorders

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 "Pharmacokinetics").

Elderly patients

Of the 362 patients treated with RYBREVANT in EDI1001 (CHRYSALIS), 41% were 65 years of age or older, and 12% were 75 years of age or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. No dosage adjustment is necessary (see “Pharmacokinetics”).

Children and adolescents (17 years of age and younger)

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

Delayed administration

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.

Contraindications

Hypersensitivity to the active substance or to any of the excipients according to the composition.

Warnings and precautions

The data described in the “Warnings and precautions” reflects the safety profile of 489 patients with locally advanced or metastatic NSCLC who received any dose of RYBREVANT monotherapy in Study EDI1001.

Infusion-Related Reactions

Infusion-related reactions occurred in 66.7% of patients treated with RYBREVANT. 98% of IRRs were Grade 1-2. 94% 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 / 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 (glucocorticoids, antihistamines, antipyretics) 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 / Administration”).

Interstitial Lung Disease

Interstitial lung disease (ILD) or ILD-like adverse reactions (e.g. pneumonitis) occurred in 2.7% 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 / Administration”).

Skin and Nail Reactions

Rash (including dermatitis acneiform), pruritis and dry skin occurred in patients treated with RYBREVANT. Most cases were Grade 1 or 2, with Grade 3 events occurring in 3.7% of patients. Rash leading to RYBREVANT discontinuation occurred in 0.2% of patients. Rash usually developed within the first 4 weeks of therapy, with a median time to onset of 14 days. Toxic epidermal necrolysis (TEN) has been reported. Treatment with RYBREVANT should be discontinued if TEN is confirmed. Paronychia occurred in patients treated with RYBREVANT. Most events were Grade 1 or 2, with Grade 3 paronychia occurring in 2.0% of patients.
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. Interrupt RYBREVANT based on severity (see “Dosage / Administration”).

Eye Disorders

Eye disorders, including keratitis (0.4%), occurred in patients treated with RYBREVANT. Other reported adverse reactions included dry eye, blurred vision, eye pruritus, lacrimation increased, visual impairment, ocular hyperemia, eyelid ptosis, and aberrant eyelash growth. 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.

Excipients

RYBREVANT contains less than 1 mmol sodium (23 mg) per 1 vial, i.e. it is almost "sodium-free".

Interactions

No drug interaction studies have been performed.

Pregnancy, lactation

Women of childbearing age

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.

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, embryo lethality, 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 must not be used during pregnancy unless the treatment with RYBREVANT is necessary because of the woman's clinical condition. If the patient becomes pregnant while taking this drug, the patient should be informed of the potential risk to the fetus.

Lactation

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

Fertility

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

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, including vision-related adverse reactions, affecting their ability to concentrate and react, it is recommended that they do not drive or use machines until the effect subsides.

Undesirable effects

The safety of RYBREVANT was evaluated in Study EDI1001, in which 489 patients were treated with amivantamab monotherapy.
The most common adverse reactions ≥ 20% were rash, IRR, nail toxicity, hypoalbuminemia, fatigue, oedema, stomatitis, constipation and nausea. The most common adverse reactions with Grade 3 and 4 were rash (3.9%), IRR (2.3%) and nail toxicity (2.0%). Serious adverse reactions in > 1% of patients included interstitial lung disease (1.4%), IRR (1.2%) and rash (1.0%). 4.1% of patients discontinued RYBREVANT due to adverse reactions. The most frequent adverse reaction (> 1%) leading to treatment discontinuation was IRR (1.6%).

Table 6 presents adverse reactions reported in all patients treated with RYBREVANT monotherapy in Study EDI1001. Adverse reactions are listed by system organ class and frequency: very common (≥ 1/10), common (≥ 1/100 to 1/10), uncommon (≥ 1/1000 to < 1/100), and rare (≥ 1/10,000 to < 1/1000). Within each frequency grouping, adverse reactions are presented in order of decreasing frequency.

Table 6: Adverse reactions reported in all patients treated with amivantamab monotherapy in Study EDI1001

System Organ Class Adverse Reaction	RYBREVANT (N=489)			
	Frequency Category	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hepatobiliary disorders				
Hypertransaminasaemia[a]	Very common	17.4	1.2	0.4
Blood alkaline phosphatase increased		11.7	0.6	0
Skin and subcutaneous tissue disorders				
Rash[b]	Very common	75.3	3.9	0
Nail toxicity[c]		46.0	2.0	0
Pruritis		18.2	0	0
Dry skin[d]		17.2	0	0
Toxic epidermal necrolysis	Uncommon	0.2	0.2	0
Injury, poisoning and procedural complications				
Infusion-related reaction	Very common	66.7	2.0	0.2
Gastrointestinal disorders				
Stomatitis[e]	Very common	23.7	0.6	0
Constipation[f]		22.7	0	0
Nausea		22.5	0.4	0
Vomiting		11.7	0.4	0
Diarrhoea		11.0	1.4	0
Abdominal pain[g]		10.2	0.6	0
General disorders and administration site conditions				
Fatigue[h]	Very common	26.2	1.2	0
Oedema[i]		25.8	1.0	0
Metabolism and nutrition disorders				
Hypoalbuminemia[j]	Very common	31.1	1.8	0
Decreased appetite		15.5	0.6	0
Hypocalcaemia		10.8	0.2	0
Nervous system disorders				
Dizziness[k]	Very common	13.1	0.2	0
Musculoskeletal and connective tissue disorders				
Myalgia	Very common	10.6	0.4	0
Eye disorders				
Other eye disorders[l]	Common	5.5	0	0
Visual impairment[m]	Common	2.7	0.2	0
Growth of eyelashes[n]		1.2	0	0
Keratitis[o]	Uncommon	0.6	0	0
Uveitis		0.2	0	0
Respiratory, thoracic and mediastinal disorders				

System Organ Class Adverse Reaction	RYBREVANT (N=489)			
	Frequency Category	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Interstitial lung disease[p]	Common	2.7	0.6	0

Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.

[a] includes Alanine aminotransferase increased, Aspartate aminotransferase increased, Hypertransaminasaemia

[b] includes Acne, Dermatitis, Dermatitis acneiform, Erythema, Erythema multiforme, Folliculitis, Impetigo, Macule, Palmar-plantar erythrodysaesthesia 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

[c] includes Ingrowing nail, Nail bed infection, Nail cuticle fissure, Nail disorder, Nail dystrophy, Nail ridging, Onychoclasis, Onycholysis, Paronychia

[d] includes Dry skin, Eczema, Eczema asteatotic, Skin fissures, Xeroderma

[e] includes Aphthous ulcer, Cheilitis, Glossitis, Lip erosion, Lip ulceration, Mouth ulceration, Mucosal inflammation, Stomatitis

[f] includes Constipation, Dyschezia

[g] includes Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Epigastric discomfort, Gastrointestinal pain

[h] includes Asthenia, Fatigue

[i] includes Eye oedema, Eyelid oedema, Face oedema, Generalised oedema, Localised oedema, Oedema, Oedema peripheral, Periorbital oedema, Periorbital swelling, Peripheral swelling, Swelling face

[j] includes Blood albumin decreased, Hypoalbuminaemia

[k] includes Dizziness, Dizziness exertional, Dizziness postural, Vertigo

[l] includes Blepharitis, Conjunctival hyperaemia, Corneal irritation, Dry eye, Episcleritis, Eye disorder, Eye inflammation, Eye pruritus, Noninfective conjunctivitis, Ocular hyperaemia

[m] includes Vision blurred, Visual acuity reduced, Visual impairment

[n] includes Eyelash thickening, Growth of eyelashes, Trichomegaly

[o] includes Keratitis, Punctate keratitis

[p] includes Interstitial lung disease, Pneumonitis

Interstitial lung disease

Interstitial lung disease or ILD-like adverse reactions have been reported with the use of RYBREVANT as well as with other EGFR inhibitors. Interstitial lung disease or pneumonitis were reported in 2.7% of 489 patients. (see “Warning / Precautions”).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Signs and symptoms

There is no information on overdosage with RYBREVANT. There has been no experience of overdosage in clinical studies. No maximum tolerated dose has been determined in a clinical study in which patients received up to 1750 mg administered intravenously.

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.

Properties/Effects

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 Exon 20 insertion mutations. 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.

Pharmacodynamics

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 also for amivantamab. 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 different studies may be misleading.
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. There are insufficient data to assess the effects of antibodies to amivantamab on the pharmacokinetics, efficacy, or safety of RYBREVANT.

Clinical efficacy

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 evaluated in 81 subjects with locally advanced or metastatic NSCLC who had EGFR Exon 20 insertion mutations, whose disease had progressed on or after platinum-based chemotherapy, and who had median follow-up of 9.7 months. Identification of an EGFR exon 20 insertion mutation was determined locally using next generation sequencing (NGS) or polymerase chain reaction (PCR) on tumour tissue or plasma samples. 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 thereafter until disease progression or unacceptable toxicity.

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. Patients with planned invasive operative procedure, recent traumatic injury, expected major surgery 6 months after the last dose of study drug were also excluded. Intracranial responses were not assessed in the CHRYSALIS study.

The median age was 62 (range: 42–84) years, with 9% of the subjects ≥75 years of age; 59% were female; and 49% were Asian and 37% were White. 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 (99%); 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%).

Efficacy results are summarized in Table 7.

Table 7: Efficacy Results for EDI1001 (CHRYSALIS)

	Prior Platinum Chemotherapy Treated (N=81)
Overall Response Rate[a,b] (95% CI)	40% (29%, 51%)
Complete response	4%
Partial response	36%
Duration of Response[a] (DOR)	
Median (95% CI), months[c]	11.1 (6.9, NE)
Patients with DOR ≥ 6 months	63%
Median Progression-Free Survival[a] (95% CI), months	8.3 (6.5, 10.9)

Median Overall Survival (95% CI), months	22.8 (17.5, NE)

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

Temporary authorisation

Due to incomplete clinical data at the time of the evaluation of the marketing authorisation application, RYBREVANT is granted a temporary marketing authorisation (Art. 9a Therapeutic Products Act). The temporary marketing authorisation is compulsorily linked to the timely fulfilment of conditions. Once these conditions have been fulfilled, the temporary marketing authorisation can be converted into a full marketing authorisation.

Pharmacokinetics

Amivantamab area under the concentration-time curve (AUC1 week) increases dose-proportionally over a dose range from 350 to 1750 mg (0.25 to 1.25 times the maximum recommended dose).

Absorption

Amivantamab pharmacokinetic parameters are summarized in Table 8.

Table 8: Pharmacokinetic Parameters

Mean (SD)	Amivantamab Dose (Weight Category)	
	1050 mg (<80 kg)	1400 mg (≥80 kg)
Maximum exposure following 5th weekly dose		
n	26[a]	8[b]
C_{max}, mcg/mL	836 (264)	655 (109)
AUC_{1week}, mcg.h/mL	94946 (35440)	76946 (14557)
AUC_{2weeks}, mcg.h/mL	153667 (61092)	121017 (28922)
AR $AUC_{1week(1st\ dose/5th\ dose)}$	2.88 (0.68)	3.03 (0.82)

[a] n=25 for AUC_{1week} and n=21 for AR $AUC_{1week\ (1st\ dose/5th\ dose)}$.
[b] n=7 for AR $AUC_{1week\ (1st\ dose/5th\ dose)}$

Amivantamab was administered as intravenous infusion once weekly for 4 weeks and every 2 weeks thereafter staring at week 5, with doses given as a split dose at the first dose.
Abbreviations: C_{max} - serum maximal concentration; AUC_{1week} and AUC_{2weeks} - area under the serum concentration-time curve one week and two weeks after the fifth dose, respectively.

Amivantamab steady state was achieved approximately 2 months into the every 2-week dosing period (by the ninth infusion) and the mean steady state accumulation was 2.44-fold.

Distribution

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

Metabolism

No data.

Elimination

The mean ± SD clearance was estimated to be 360 ± 144 mL/day and the mean ± SD estimated terminal half-life was 11.3 ± 4.53 days.

Kinetics in specific patient groups

Hepatic impairment

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 was not examined.

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 was not examined.

Elderly patients (65 years of age and older)

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

Children and adolescents (17 years of age and younger)

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

Gender

The clearance of amivantamab was 24% higher in males than in females; however, this difference was assessed as not clinically meaningful.

Weight

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

Preclinical data

In repeat-dose toxicity studies in cynomolgus monkeys, amivantamab was well-tolerated at weekly doses up to 120 mg/kg intravenously for 6 weeks or 3 months (~6-8x 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.

Carcinogenicity and Mutagenicity

No animal studies have been performed to establish the carcinogenic and genotoxic potential of amivantamab.

Reproductive toxicity

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

Other information

Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in “Dosage/ Administration”.

Shelf life

Unopened vials:
Do not use this medicine after the expiry date ("EXP") stated on the pack (see expiry date on the outer pack).

Shelf life after opening

After dilution:
The diluted preparation for infusion is not preserved.
Chemical and physical stability of the diluted solution has been demonstrated for 10 hours at 15-25 °C. For microbiological reasons, the diluted solution should be used immediately, unless the dilution has taken place in controlled and validated aseptic conditions. If the solution is not used immediately, storage times and conditions are the responsibility of the user.
Administer diluted solutions within 10 hours (including infusion time) at room temperature (15°C to 25°C) and in room light.

Special precautions for storage

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

Do not freeze.
Store in the original package in order to protect from light.
For storage conditions after dilution of the medicinal product, see “Shelf life”.
Keep out of sight and reach of children.

Instructions for handling

Preparation for Administration

RYBREVANT solution must be diluted and prepared for intravenous infusion by a healthcare professional using aseptic technique (see also “Other Information”).

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/Administration” and table below). Each vial (7 ml) of RYBREVANT contains 350 mg of amivantamab.

Recommended Dose	Number of vials
1050 mg	3
1400 mg	4

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.

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

Authorisation number

68380 (Swissmedic).

Packs

Cartons with 1 single-use vial of 350mg/7mL [A].

Marketing authorisation holder

Janssen-Cilag AG, Zug, ZG

Date of revision of the text

January 2022