Taiwan Food and Drug Administration

Assessment Report

Trade Name：肺倍恩注射劑 50 毫克/毫升

Rybrevant Concentrate for Solution for Infusion 50mg/ml

Active Ingredient：Amivantamab

License Number：MOHW-BI 001177

Applicant：嬌生股份有限公司

Approval Date：2021/9/24

Indication：

Rybrevant 單一療法適用於罹患帶有表皮生長因子受體(EGFR) exon 20 插入突變之局部晚期或轉移性非小細胞肺癌(NSCLC) 的成人病人，作為含鉑類化學療法治療失敗後之治療。

適應症為依據替代指標(整體反應率和反應持續期間)採加速核准的方式，後續需執行確認性試驗以證明確實達到臨床上的效益。

Indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, after failure of platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1. Background Information

Trade Name	肺倍恩注射劑 50 毫克/毫升 / Rybrevant Concentrate for Solution for Infusion 50mg/ml
Active Ingredient(s)	Amivantamab
Applicant	嬌生股份有限公司
Dosage Form & Strengths	注射劑 50 毫克/毫升
Indication	Rybrevant 單一療法適用於罹患帶有表皮生長因子受體(EGFR) exon 20 插入突變之局部晚期或轉移性非小細胞肺癌(NSCLC) 的成人病人，作為含鉑類化學療法治療失敗後之治療。 適應症為依據替代指標(整體反應率和反應持續期間)採加速核准的方式，後續需執行確認性試驗以證明確實達到臨床上的效益。 Indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, after failure of platinum-based chemotherapy. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
Posology	請參閱仿單。
Pharmacological Category ATC Code	L01FX18

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

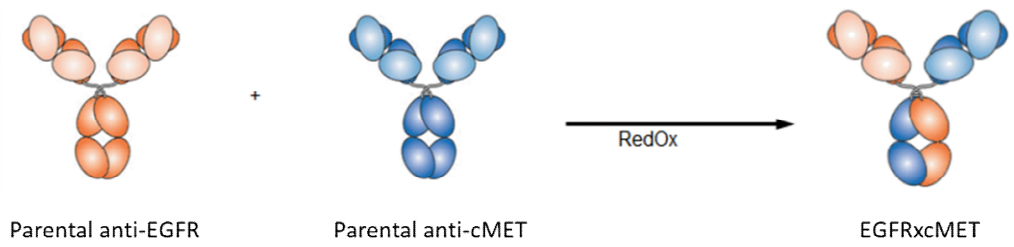
2.1.1 Drug substance

Amivantamab (JNJ-61186372, also known as CNTO 4424) is a low-fucose, fully-human,

IgG1-based EGFR-MET bispecific antibody with immune cell-directing activity that targets tumor with activating and resistance EGFR mutations and MET mutations and amplifications. Amivantamab binds to the extracellular domains of EGFR and MET.

The amivantamab drug substance (DS) is manufactured at Biogen Inc, Research Triangle Park, in North Carolina, USA (Biogen, manufacturing Stages 1-5), and Janssen Sciences Ireland UC in Cork, Ireland (JSI, manufacturing Stages 6-14).

Amivantamab is produced by cultivation of recombinant CHO cells with specificity for EGFR and cMET and has a molecular mass of 148 kDa for the major glycoform. Amivantamab consists of 2 heavy chains (HC) and 2 light chains (LC), joined by disulfide bonds. It is prepared by controlled reduction and oxidation of the parental anti-EGFR and anti-cMET monospecific antibodies (mAbs) resulting in an exchange of the Fab arms as depicted in figure below. The Fab arm exchange is facilitated by amino acid substitutions in the CH3 domains to enable preferential refolding of the heterodimer. Detailed description of the origin, history and preparations of cell banks including MCBs, WCBs and EPCs were provided. Adventitious and endogenous agent safety testing and identity for cell banks were conducted based on the recommendations in ICH guidance. Raw materials of direct and indirect biological origin were also justified.



Characterization studies were presented including primary and higher-order structure, glycosylation, oxidation, disulfide structure, charge and size variants, and biological activity of target binding, as well as product variants and process-related impurities. The exclusion for some process-related impurities from routine testing was appropriately justified. Manufacturing process with in-process controls, process development histories, comparability studies, process validation, specification, analytical methods and validation, batch analyses, reference materials and virus clearance studies, were provided abundantly to demonstrate the quality and consistency of Amivantamab using commercial process.

Long-term, accelerated, and stress stability studies have been carried out for Amivantamab batches. The stability studies are derived from Amivantamab batches produced with the commercial process.

2.1.2 Drug product

Rybrevant® is supplied as a sterile, 50 mg/mL liquid concentrate for infusion. Each vial contains 350 mg of amivantamab in a 7.0 mL nominal fill volume and an excess volume of 0.5 mL. The DP is intended for administration by the intravenous (IV) route after dilution in commercially available 5% dextrose (glucose) or 0.9% Normal Saline (NS). Rybrevant® is manufactured at Cilag AG in Schaffhausen, Switzerland.

The composition of DP is listed. The excipients for DP are complied with USP-NF, Ph. Eur., and/or JP compendia specifications. There are no novel excipients in the DP. No excipients of human or animal origin are used in the DP.

DP manufacturing process and formulation development were described appropriately. Adequate justifications for potential impurities and the container closure integrity were provided to support the suitability of the container closure system. The compatibility data is submitted adequately. Manufacturing process within process controls, process validation, specification and batch analyses were provided and showed that the manufactures of Rybrevant® are controlled properly and consistently.

The release specification and stability specification for Rybrevant® include appearance, general characteristic properties, quantity, identity, purity/impurity, potency by cell-based bioassay and safety. The specifications of Rybrevant® are generally acceptable.

Stability studies, conducted under long-term storage, accelerated and stress conditions, and in-use stability studies could support the storage and on-site usage for Rybrevant®. The current commercial scale data of long-term stability studies supports the shelf life of Rybrevant® for 12 months under the storage condition of 5±3°C, protected from light.

In conclusion, information on the intermediates, drug substance and finished drug product is regarded as appropriate to support the quality of Rybrevant®.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Rybrevant® (Amivantamab) is a drug for treating adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) exon 20 insertion mutations, after failure of platinum-based chemotherapy. Amivantamab is a low-fucose, fully human bispecific IgG1-based antibody directed against the EGFR and MET. It binds to EGFR and MET on the surface of tumor cells and induces antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) with macrophages and natural killer cells to inhibit tumor growth. The

in vitro pharmacology studies demonstrated that amivantamab inhibited human EGFR and MET activities and enhanced Fc-dependent effector function. The *in vivo* pharmacology studies confirmed the results from *in vitro* studies and indicated that amivantamab exhibited anti-tumor effects on the tumor cells presenting some mutations resistant to the third-generation TKIs. Safety pharmacology was evaluated in the repeated-dose toxicity studies in monkeys.

2.2.2 Toxicological Studies

The pivotal toxicity studies were repeated-dose studies in monkeys for 1 to 3 months. Most findings were mild and recoverable. No significant findings in safety pharmacology endpoints and local tolerance were observed. Although some animals produced anti-drug antibodies, the results might not be expected to predict the human immunogenic response.

Genotoxicity and carcinogenicity studies were not conducted since amivantamab is a large molecule intended to treat advanced cancer. Reproductive and developmental toxicity studies were not conducted. No adverse findings on reproductive organs were observed in the repeated-dose toxicity studies. The previous studies with small-molecule inhibitors of the EGFR and MET suggested that disruption of these pathways might impair embryo-fetal development, postnatal development, and survival. Therefore, the administration of amivantamab could be expected to pose a significant risk to pregnant women and fetuses. Amivantamab was compatible with human blood and serum.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Rybrevant® contained 350 mg amivantamab in 7 ml vial (50 mg/ml), the active substance is a bispecific antibody that binds to the extracellular domains of EGFR and MET. Over the range of 350 mg ~ 1750 mg, the exposure of amivantamab increased dose-proportional. Following the proposed posology, steady state can be achieved on Cycle 4 Day 1 (9th infusion), and the accumulation ratio was 2.4 at 1050 mg dose. Based on the population PK analysis, the estimated volume of distribution was 5.13L, clearance was 360 (± 144) mL/day, and the terminal half-life was 11.3 days.

2.3.2 Interaction Studies

There was no dedicated drug-drug interaction study for amivantamab as amivantamab is a monoclonal antibody.

2.3.3 Special Populations

According to population PK analysis, age, mild [(total bilirubin ≤ ULN and AST >ULN) or (ULN< total bilirubin ≤ 1.5×ULN)] hepatic impairment, mild (60≤ CLcr <90

mL/min) and moderate (29≤ CLcr <60 mL/min) renal impairment had no impact on amivantamab PK. Male have higher CL (↑ 24%) than female; thus, higher exposure was predicted in female (AUC0-14 day,ss: ↑ 34%; Ceoi,ss: ↑ 24%). This was not considered clinically meaningful differences. Body weight affected the clearance and volume of distribution. In same dose level group, subjects with higher body weight (≥80 kg) had lower exposure about 30% ~ 40% than subjects with lower body weight (<80 kg). Also, subjects with a body weight < 80 kg dosed at 1050 mg and subjects with a body weight ≥80 kg dosed at 1400 mg had similar exposure. Thus, the weight-based dosing regimen was chosen.

Overall, the pharmacokinetic studies met the minimum requirements to support the marketing authorization.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Amivantamab is currently being studied in the Phase 1 CHRYSALIS (Study EDI1001) study, in subjects with locally advanced or metastatic NSCLC. This study is a first-in-human, open-label, multicenter Phase 1 study to evaluate the safety, PK, and preliminary efficacy of Amivantamab as a monotherapy or in combination with lazertinib. No DLTs were reported and no MTD were identified during dose escalation part. Amivantamab had no apparent dose-dependent adverse events in the dose range tested. Population PK model simulation suggested that equivalent exposures were attained by fixed-dose based adjusted on body weight. The posology of 1050 mg for subjects <80 kg body weight or 1400 mg for subjects >80 kg body weight, at a regimen of Q1W for Cycle 1 and Q2W for Cycle 2 has been selected as RP2D.

The primary efficacy population consisted of 81 subjects with Exon 20ins NSCLC who were treated at the amivantamab RP2D, and who had progressed on or after prior platinum chemotherapy. These subjects had a median age of 62 years (range: 42-84); 59.3% were female, and 49.4% were Asian. Forty-three (53.1%) of these subjects had never smoked and 75.3% had Stage IV disease at initial diagnosis. The median time from diagnosis of metastatic disease to the first dose of amivantamab was 14.2 months (range: 0.69-116.40) and the median number of lines of prior therapy was 2 (range: 1-7). About prior therapy, 45.7% of subjects in this population had received prior immunotherapy, and 24.7% had received prior TKI therapy. The median duration of treatment was 5.1 months. The BICR-assessed confirmed ORR as of the 08 October 2020 cutoff at RP2D primary efficacy population was 39.5% (95% CI: 28.8%, 51.0%). The BICR-assessed median DOR was 11.1 months (95% CI: 6.90, NE) with the longest response reported as 21.7 months. Among the BICR responders, the median duration of treatment was 10.1 months and 62.5% had a DOR of ≥6 months. With a median follow up of 9.7 months, the median PFS based on BICR response

assessment at RP2D primary efficacy population was 8.28 months (95% CI: 6.51, 10.87). The median OS was 22.77 months (95% CI: 14.59, NE), with 71.6% of subjects censored.

2.4.2 Safety Results

Among 258 patients who received at least 1 dose of amivantamab monotherapy at P2RD, the median follow up was 6.6 months (maximum, 33.61). Grade 3 or higher TEAEs were experienced by 101 (39.1%) patients. The most frequently reported (>20%) TEAEs included infusion-related reactions (IRR, 64.7%) and the on-target events linked to EGFR inhibition (paronychia [40.3%], rash [36.0%], and dermatitis acneiform [37.6%]), and the on-target event linked to MET inhibition (hypoalbuminemia [24.4%]). Constipation (22.5%), and nausea (21.3%) were also reported. Grade 3 or higher TEAEs in this population that were reported in at least 2% of subjects were dyspnea (4.3%), hyponatremia (3.1%), pneumonia (3.1%), hypokalemia (2.7%), pulmonary embolism (2.7%), and IRRs (2.3%).

Serious TEAEs were reported for 79 subjects (30.6%) in the all treated at RP2D population, of which 13 subjects (5.0%) had an event that was assessed by the investigator as related to amivantamab. Serious TEAEs (any relationship) reported in ≥2% of subjects in this population were pneumonia (3.5%) and dyspnea (3.5%), with most other events reported in 1 or 2 subjects each (frequency <1%). There were 13 deaths and all of them were considered unrelated to amivantamab. Infections(n=6) and respiratory(n=5) events were the most common TEAEs leading to death.

IRR was usually mild or moderate, non-serious and not treatment limiting. Most of IRR occurred at the first infusion and had a median onset time of just under an hour. Once managed well, very few subjects experienced again in later cycles. The known on-target effects of EGFR and MET inhibitors, including dermatitis, paronychia, rash, and hypoalbuminemia, were also observed with similar clinical manifestation.

Among the 362 subjects who had received amivantamab, 3 (1.0%) subjects were considered positive for antibodies to amivantamab post-dose. No neutralizing effect was found in these 3 subjects.

2.5 Bridging Study Evaluation

In the subgroup analysis of Study EDI1001, the amivantamab exposure in Taiwanese, East Asian was comparable with all subjects. Based on population PK analysis, no notable differences were seen in the PK data among Taiwanese, East Asian and all subjects. No dose adjustment was required for Taiwanese.

Among the patients received prior chemotherapy and P2RD amivantamab monotherapy in

Study EDI1001, 53(46.5%) subjects were East Asians, including 7 Taiwanese. Their baseline characteristics were similar to the overall population. Subgroup analysis demonstrated antitumor activity (ORR and CBR) consistent with the responses observed in the East Asians and the overall population. The BICR-assessed confirmed ORR and CBR at East Asian population was 40.5% (95% CI: 24.8%, 57.9%) and 73.0% (95% CI: 55.9%, 86.2%), respectively. The safety profile of East Asian subgroup was consistent with those reported for overall population.

2.6 Conclusion

Amivantamab as the treatment of adult patients with locally advanced or metastatic NSCLC and with activating EGFR Exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy demonstrated a favorable risk-benefit profile with adequate evidence to recommend accelerated approval. Post-marketing confirmatory study is required to verify its clinical benefit.

3. Post-Marketing Requirements

- Submit the final report of Study CHRYSALIS (Study EDI1001) after study completion.
- Submit the interim report and final report of the confirmatory trial: Study PAPILLON (Study NSC3001) while available.
- Provide drug consumption data and estimate drug demand in Taiwan during the 5 years after approval to fulfill the requirement of Pediatric or Rare Severe Disease Designation（小兒或少數嚴重疾病藥品審查認定要點）.