Cost-effectiveness of amivantamab (Rybrevant®) for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating EGFR Exon 20 insertion mutations, after failure of platinum-based therapy.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of amivantamab (Rybrevant®). Following assessment of the Applicant's submission, the NCPE recommends that amivantamab (Rybrevant®) not be considered for reimbursement. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the NCPE to carry out an evaluation of the Applicant's (Janssen Ireland) Health Technology Assessment of amivantamab (Rybrevant®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.
Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **April 2023**

Summary

In August 2022, Janssen Ireland submitted a dossier of clinical, safety and economic evidence for amivantamab (Rybrevant®) for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations (Exon20in), after failure of platinum-based therapy. Amivantamab received conditional marketing authorisation from the EMA on 9 December 2021. Amivantamab is a fully human, bispecific antibody that targets the proto-oncogenes EGFR and MET. Amivantamab targets these receptors on the surface of tumour cells, allowing for destruction of these tumour cells by immune effector cells. Amivantamab is administered as an intravenous infusion; one 7mL vial of concentrate for solution for infusion contains 350mg of amivantamab. Amivantamab is administered once weekly for the first four weeks of treatment and then once every two weeks until disease progression or unacceptable toxicity. Dosing of amivantamab is weight-based; adults weighing less than 80kg are administered 1,050mg per dose and adults weighing 80kg or more are administered 1,400mg per dose. Amivantamab is the first licensed treatment for patients with advanced NSCLC with activating EGFR Exon20in. The current standard of care comprises a number of drugs, herein referred to as 'physician's choice', used to treat advanced or metastatic NSCLC, not specifically with activating EGFR Exon20in, following progression with platinum-based chemotherapy. Physician's choice consists of immunotherapies, oral EGFR tyrosine kinase inhibitors and non-platinum-based chemotherapy. Testing for EGFR mutations is currently part of routine care for patients diagnosed with advanced NSCLC in Irish clinical practice. Reimbursement is sought on the Oncology Drug Management Scheme.

1. Comparative effectiveness of amivantamab

The efficacy and safety of amivantamab is assessed in the CHRYSALIS study which is an ongoing phase Ib/II single arm, open-label study in adult patients with advanced NSCLC. This is a multi-cohort study; the cohort of relevance to this submission is Cohort D+ (n=114; comprises patients with locally documented NSCLC with activating EGFR Exon20in who were treated with amivantamab monotherapy at the recommended phase II dose prior to 4 June

2020 data cut-off, had three or more disease assessments and had received prior platinum-based chemotherapy). As such, only efficacy results of relevance to cohort D+ (the expanded efficacy population) are presented henceforth. The primary endpoint of the study was the overall response rate (ORR) based on investigator assessment and blinded independent central review (BICR) assessment. Key secondary endpoints included progression-free survival (PFS) and overall survival (OS). Efficacy data with a cut-off date of 30 March 2021 underpins conditional regulatory approval. Based on investigator assessment, the ORR for amivantamab was 36.8% (95% confidence interval (CI) 28 to 46.4), comprising entirely of participants who had a partial response (no patients had a complete response). Using BICR assessment, the ORR was estimated to be 43% (95% CI 33.7 to 52.6), comprising 2.6% of patients with a complete response. The median PFS was 6.9 months and 6.7 months based on investigator and BICR assessment, respectively. The Applicant provided more mature OS data in the HTA submission, with a data cut-off date of 7 March 2022. The median OS based on this data cut was 23.13 months (95% CI 17.74 to 29.24). Treatment with amivantamab could continue beyond disease progression with 22% of patients continuing treatment beyond disease progression. The Committee for Medicinal Products for Human use (CHMP) stated that PFS and OS estimates are to be used for descriptive purposes only and cannot be used as claims of drug effect. The CHMP highlighted that while the ORR demonstrated is considered good, in the absence of a very high ORR, the demonstration of benefit in terms of PFS and OS is needed to confirm efficacy. Conditional approval was granted subject to the results from the confirmatory PAPILLON study, although the Review Group highlight that this study evaluates amivantamab in combination with chemotherapy for the first-line (or later) treatment of advanced NSCLC with Exon 20in. Therefore, efficacy results will not be of relevance to the current indication.

Given a lack of direct comparative evidence, indirect comparative methods are required to inform the comparative effectiveness analysis between amivantamab and physician's choice. The systematic literature review (SLR) conducted by the Applicant did not identify any trials suitable for an indirect treatment comparison (ITC). Data were sourced from seven real-world evidence (RWE) datasets across the EU and US (EU+US). Using key prognostic variables identified from a SLR and based on the available data within the EU+US RWE data

source, the Applicant weighted the available data in the EU+US RWE datasets using a propensity score-inverse probability weighting (IPW-PS) approach. The targeted estimand was the average treatment effect on the treated population (ATT) which re-weights the physician's choice arm to achieve a similar baseline distribution to the amivantamab-treated population in the CHRYSALIS trial, thus estimating the relative treatment effect in the trial population. The results of this unanchored treatment comparison suggest that amivantamab reduces the hazard of disease progression by 41% compared with physician's choice and that the hazard of death is reduced by 53% compared with physician's choice. However, given the lack of transparency regarding selection of patients within RWE datasets and the limitations of the analytic approach, the Review Group advise that extreme caution should be exercised in the interpretation of these results.

The Review Group identified a number of limitations of the comparative effectiveness analysis including: the non-systematic selection of RWE data sources; comparing trial data to observational data from a number of heterogenous RWE sources; and high risk of bias due to missing confounders in the IPW-PS model.

2. Safety of amivantamab

Safety data from the CHRYSALIS trial population with Exon 20in NSCLC who received amivantamab at the licensed dose (n=153) were included in the safety analysis, with a data cut-off date of 30 March 2021. In total, 41.8% of the safety population experienced a grade three or higher adverse event (AE) and 28.8% experienced a serious AE. The most common grade three AEs experienced were pulmonary embolism (4.6%) and hypokalaemia (3.9%). Infusion-related reactions (IRRs) were common (63.4%) although the vast majority occurred at the first infusion (94.7%), with 0.1% of patients experiencing IRRs from cycle two onwards. Pre-infusion medication can be administered to reduce the risk of IRRs with amivantamab treatment.

3. Cost effectiveness of amivantamab

Methods

A three-state partitioned survival model was submitted by the Applicant. The treatment effects captured by the cost-effectiveness model (CEM) were the delay of disease progression and death. The key efficacy inputs to the model were PFS and OS. The patient population included in the CEM is reflective of the expanded efficacy population in the CHRYSALIS trial. Patients with Exon 20in who received platinum-based chemotherapy as part of adjuvant treatment at an earlier stage of disease and subsequently progress to advanced disease would be eligible for treatment with amivantamab as per the licence. These patients were not included in the CHRYSALIS trial and as such, there is no efficacy data available for these patients. Clinical opinion, obtained by the Review Group, indicated that these patients represent a small proportion of the eligible population currently. However, the Review Group note that treatment pathways in NSCLC are rapidly evolving. In the Applicant base case, the distribution of drugs in physician's choice (for costing purposes) is estimated based on clinical opinion received by the Applicant. In the NCPE adjusted base case, the distribution of drugs in physician's choice is estimated based on the distribution of drugs in the EU+US RWE dataset as this is reflective of the clinical efficacy data for the physician's choice arm and has better alignment with Irish clinical practice based on recent clinical opinion received by the Review Group.

Individual patient data (IPD) from the CHRYSALIS trial were used to inform Kaplan Meier curves for amivantamab, whereas IPW-adjusted IPD from the EU+US RWE data source were used to construct Kaplan Meier curves for physician's choice. In this way, relative efficacy estimates from the unanchored treatment comparison were not implemented directly in the CEM. For PFS, the Review Group considered it more consistent to use investigator assessments across both treatment arms, given that BICR assessments were not available in EU+US RWE dataset. The Applicant extrapolated the PFS curve from the CHRYSALIS trial for amivantamab while the Kaplan-Meier data for the EU+US RWE data source was used directly for the physician's choice arm in the base case analysis. Given the lack of scheduled assessments in the EU+US RWE data source, the Review Group considered it more appropriate to extrapolate PFS data for both treatment arms and apply the same distribution (Lognormal). The Review Group believes that there are no strong justifications for applying alternative distributions to each respective treatment arm. For OS, the Applicant extrapolated the OS data using the Weibull distribution and used the Kaplan-

Meier data for the physician's choice arm. The Review Group considered this to be reasonable given the maturity of the EU+US RWE OS data. The Applicant assumed that time on treatment for both treatment arms was equivalent to the time to progression for each respective treatment. The Review Group considered it more appropriate to use the time to treatment discontinuation (TTD) curve from the CHRYSALIS trial to model treatment duration for amivantamab. TTD data were not available for the physician's choice arm, although time-to next-treatment (TTNT) data were available. The Review Group did not consider TTNT data to be an appropriate proxy for TTD data and PFS data was used to model treatment duration in the physician's choice arm.

Health-related quality of life (HRQoL) data were only collected for a small proportion of patients in the CHRYSALIS study (n=26), with the number contributing to HRQoL assessments decreasing to one by cycle 14. As such, there is a lack of HRQoL data from the CHRYSALIS trial. The Applicant conducted a SLR to identify health-state utility values (HSUVs) that could be used in the CEM; however, he Applicant did not use the HSUVs that were identified. Instead, HSUVs used in the CEM were sourced from a National Institute for Health and Care Excellence (NICE) technology appraisal of nivolumab for the treatment of advanced non-squamous NSCLC after chemotherapy (TA713). The Review Group conducted scenario analyses using alternative HSUVs identified in the SLR.

Results

The results of the Applicant base case deterministic cost-effectiveness analysis are presented in Table 1.

Table 1: Applicant base case incremental cost-effectiveness results [a,b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Physician's Choice	69,857	0.89	-	-	-
Amivantamab	145,044	1.39	75,187	0.50	150,242

Abbreviations: ***QALY****: quality adjusted life years;* ***ICER****: incremental cost-effectiveness ratio*

[a] Corresponding probabilistic ICER using 5,000 iterations =€153,770/QALY. Figures in the table are rounded, and so calculations may not be directly replicable

[b] A Framework Agreement rebate of 7.75% has been applied, where relevant. A discount rate of 4% is applied to costs and outcomes.

Results of the NCPE-adjusted base case are presented in Table 2. The Review Group highlight that the changes made in the NCPE adjusted base case do not overcome the major

limitations of the clinical evidence for amivantamab and the considerable uncertainty associated with the comparative effectiveness analysis.

Table 2: NCPE adjusted base case incremental cost-effectiveness results[a,b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Physician's Choice	63,298	0.88			
Amivantamab	162,365	1.42	99,067	0.54	183,181

*Abbreviations: **QALY**: quality-adjusted life year: **ICER**: incremental cost effectiveness ratio*

[a] Corresponding probabilistic ICER using 5,000 iterations =€181,609/QALY. Figures in the table are rounded, and so calculations may not be directly replicable.

[b] A Framework Agreement rebate of 8.25% has been applied, where relevant. A discount rate of 4% is applied to costs and outcomes.

The probability of cost-effectiveness for amivantamab versus physician's choice (in both the Applicant base case and the NCPE-adjusted base case analyses) was 0% at a threshold of €20,000/QALY and €45,000/QALY, respectively. Deterministic sensitivity analyses indicated that the most influential parameters in the model related to OS modelling and the cost of amivantamab treatment in subsequent cycles following the initial treatment cycle. In scenario analyses of the NCPE adjusted base case, the incremental cost-effectiveness ratio (ICER) increased when alternative treatment duration approaches were assumed for amivantamab. The Review Group estimate that a total rebate of 78% on the price to wholesaler (PtW) is required to reduce the NCPE-adjusted base case ICER below the €45,000/QALY threshold. However, a total rebate in excess of 90% is required to reduce the ICER below €20,000/QALY, which may be more appropriate for decision-making given the substantial uncertainty regarding the comparative effectiveness of amivantamab.

4. Budget impact of amivantamab

The PtW of one 7mL vial containing 350mg of amivantamab is €1,325.99. Based on the Applicant's assumption that time to progression is equivalent to time on treatment (mean of 10.1 months), the mean treatment course cost, per patient of amivantamab is estimated to be €116,290.76 (including VAT) and €92,981.84 (excluding VAT). Based on the mean TTD in the NCPE adjusted base case (12.04 months), the Review Group estimate the mean treatment course cost, per patient, of amivantamab to be €136,914.51 (including VAT) and €109,471.95 (excluding VAT).

The budget impact model has been reviewed by the Review Group. Many of the inputs are very uncertain and there is considerable uncertainty associated with the budget impact

estimates. The Applicant estimates that 10 patients will be treated with amivantamab in year one, reducing to four patients annually in years two to five, inclusive. The Review Group conducted an exploratory budget impact analysis which uses alternative assumptions based on more recent data received from the National Cancer Registry of Ireland (NCRI) and clinical opinion obtained by the Review Group. This exploratory analysis indicates that 33 patients could be treated with amivantamab in year one, reducing to between 12 and 13 patients annually between years two and five. The Review Group highlight the results of the NCPE exploratory budget impact analysis are likely to represent the upper range of the potential budget impact of amivantamab.

In the Applicant budget impact analysis, the cumulative five-year gross drug budget impact is estimated to be €3.24 million (including VAT) and the cumulative five-year net drug budget impact is estimated to be €2.08 million (including VAT). In the NCPE exploratory budget impact analysis, the cumulative five-year gross drug budget impact is estimated to be €10.91 million (including VAT) and the cumulative five-year net drug budget impact is estimated to be €8.74 million (including VAT)

5. Patient organisation submission

A patient organisation submission was not received during the course of this assessment.

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that amivantamab not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

* This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.