NCPE Assessment

Summary

Amivantmab (Rybrevant®)

HTA ID: 24032

10 March 2026

Applicant: Johnson and Johnson Innovative Medicine

Amivantamab in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) exon 20 insertion mutations

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of amivantamab (Rybrevant®) in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced non-small cell lung cancer with activating epidermal growth factor receptor exon 20 insertion mutations.

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

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Johnson and Johnson Innovative Medicine) Health Technology Assessment of amivantamab (Rybrevant®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative 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.

Summary

In April 2025, Johnson and Johnson Innovative Medicine submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of amivantamab (Rybrevant®), in combination with carboplatin and pemetrexed, for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) exon 20 insertion (exon20ins) mutations. Johnson and Johnson Innovative Medicine is seeking reimbursement of amivantamab on the Oncology Drug Management System.

Amivantamab is a fully human, bispecific antibody that targets EGFR and mesenchymal–epithelial transition (MET) mutations. Amivantamab has a triple mechanism of action. It inhibits tumour growth through inhibition of ligand binding, EGFR/MET receptor degradation, and by inducing cellular cytotoxicity and trogocytosis. Amivantamab is administered by intravenous infusion. For this indication, it is given in combination with carboplatin and pemetrexed (ACP). Dosing is weight based. Amivantamab and pemetrexed are recommended to be given until disease progression or unacceptable toxicity. Carboplatin is administered for four to six treatment cycles.

EGFR exon20ins mutations are rare, affecting approximately 1.3% of patients with NSCLC in Ireland. They demonstrate resistance to drugs typically prescribed for patients with EGFR mutations. Standard of care includes platinum-based chemotherapy (typically carboplatin in combination with pemetrexed [CP]) given either alone or in combination with pembrolizumab. Pembrolizumab monotherapy is sometimes considered but is less commonly prescribed.

1. Comparative effectiveness of amivantamab

The efficacy and safety of ACP was informed by PAPILLON, which is an ongoing, phase III, randomised, open-label study. Eligible participants were adults with untreated advanced or metastatic NSCLC with EGFR exon20ins who were randomised to receive either ACP (n=153) or CP (n=155). The primary endpoint was progression-free survival (PFS) as determined by blinded independent central review. Overall survival (OS) was a key secondary endpoint. Health-related quality of life (HRQoL) outcomes were also collected. Participants were permitted to continue study treatment after confirmed disease progression, at the

discretion of the investigator, if it was considered that continued clinical benefit was being derived. Participants in the CP arm were permitted to crossover to receive amivantamab monotherapy following disease progression. Study completion is anticipated late 2026.

Baseline demographic and clinical characteristics of the PAPILLON study population were balanced between treatment arms. The median age was 62 years, 58% were female, 61% were Asian and 36% were White. The majority of participants were from either Asia or the US; less than 25% of participants were from Europe. The Review Group had concerns regarding generalisability of the PAPILLON study population to patients in Ireland.

At the first interim analysis (03 May 2023), with a median follow-up of 14.9 months, a statistically significant benefit in PFS of 4.7 months was observed in favour of ACP (hazard ratio (HR) 0.40, 95% confidence interval (CI) 0.30 to 0.53). At a subsequent interim analysis (31 October 2023), with a median follow-up of 20.9 months, ACP demonstrated an improvement in OS compared to CP alone (HR 0.76, 95% CI 0.50 to 1.14); however, this was not statistically significant. The Review Group noted that treatment crossover, from CP to amivantamab monotherapy upon disease progression in the comparator arm, may have confounded OS results; the magnitude of uncertainty is unclear. OS data remains immature. There were no statistically significant differences in EQ-5D-5L scores recorded between the ACP and CP arms. However, there was a high proportion of missing data observed across both treatment arms, and disparities in the proportion of missing data observed between treatment arms. This, together with the open-label design of PAPILLON, may have biased results.

Outcomes from PAPILLON informed comparative efficacy of ACP versus CP. In the absence of direct comparative evidence for ACP versus the other comparators, unanchored indirect treatment comparisons (ITCs) were performed. A systematic literature review (SLR) did not identify any suitable trials to inform efficacy of the comparators. Consequently, clinical efficacy of pembrolizumab in combination with cisplatin and pemetrexed (pembrolizumab-CP) and pembrolizumab monotherapy were informed by data from four real-world evidence (RWE) data sources: two from Europe and two from the US. The US data sources contained the majority of representative patients. The Review Group considered the selection of RWE data sources was non-systematic and may have introduced bias. A large European database, which contained data pertaining to more than 200 patients with EGFR exon20ins mutations

was not included; its exclusion was considered an important limitation.

To control for confounding, a matching adjusted indirect comparison approach was used for the analysis of ACP versus pembrolizumab-CP. Individual participant data from RWE were reweighted, using propensity score methods (IPTW: inverse probability treatment weighting), to align with the PAPILLON population. For this analysis, eleven potential confounders were identified by an SLR. The Review Group noted that only four of the eleven confounders were adjusted for in the analysis. Propensity score weighting was not performed for pembrolizumab monotherapy due to the small sample size (n=20). Furthermore, five of the 20 patients received immunotherapy treatment other than pembrolizumab. Relative treatment effects for OS and time to next treatment were estimated as HRs. Time to next treatment was used as a proxy for PFS, as PFS was not measured in the RWE data sources. The Applicant used the average treatment effect on the treated population (ATT) estimand. The key limitation of the ATT estimand was that it measured the treatment effect of amivantamab in the PAPILLON population, which the Review Group had concerns regarding generalisability to the Irish patient population. Additionally, one observation appeared to have an extreme propensity score weight, which could bias the results. Alternative options included the average treatment effect (ATE) estimand and the truncated ATT estimand. The ATE estimand provided a measure of treatment effect across the entire population (PAPILLON and RWE sources). This would have been preferable to the Review Group due to uncertainty as to whether the PAPILLON population or the RWE population was more generalisable to the Irish patient population. However, there was an imbalance in one of the confounders which would have resulted in a biased comparison. Consequently, the Review Group maintained the ATT estimand. However, due to concerns about extreme propensity score weights biasing the comparison, the Review Group considered the truncated ATT estimand to be more appropriate. Cost-effectiveness results were highly sensitive to the choice of estimand and the uncertainty associated with them is compounded by these limitations.

Results of the ITC suggested that ACP was associated with statistically significant improvements in disease progression and OS compared to pembrolizumab-CP and pembrolizumab monotherapy. Results were highly sensitive to truncation of weights and choice of estimand. All HR estimates were uncertain with wide confidence intervals. Considering the lack of transparency regarding the selection of RWE data sources, in

addition to other limitations identified with the ITC, results should be interpreted with caution.

Limitations of the comparative effectiveness analysis identified by the Review Group included: comparison of trial data to RWE data from heterogeneous sources; concerns regarding generalisability of the PAPILLON and RWE populations to the Irish population; small sample sizes from the RWE data sources; assumption of comparable efficacy between immunotherapies for the pembrolizumab monotherapy arm.

2. Safety of amivantamab

The safety of amivantamab for this indication was informed by the safety analysis set for the PAPILLON trial at the May 2023 interim analysis (ACP arm n=151; CP arm n=155). The majority of participants experienced one or more adverse events (AEs) with 75.5% and 53.5% of participants in the ACP and CP arms experiencing a grade ≥3 AE, respectively. The most commonly reported grade ≥ 3 AEs included neutropenia (33.1% of participants receiving ACP versus 22.6% of participants receiving CP), infection (20.5% versus 7.1%) and rash (11.3% versus 0%). Pyrexia and haemorrhoids were identified as new AEs associated with amivantamab; venous thromboembolism was identified as a new AE associated with ACP. Special warnings for amivantamab include infusion-related reactions, interstitial lung disease (ILD), eye disorders, and skin and nail reactions. Amivantamab should be withheld if ILD or ILD-like adverse reactions (for example, pneumonitis) are suspected. Treatment should be permanently discontinued if ILD or ILD-like reactions are confirmed.

3. Cost effectiveness of amivantamab

Methods

Cost-effectiveness was assessed, from the perspective of the HSE, using a partitioned survival model. The cost-effectiveness model (CEM) included three mutually-exclusive health states: progression-free (PF), progressed disease (PD), and Death. These health states captured PFS and OS, which were endpoints in the PAPILLON study. In each cycle, patients accrued quality-adjusted life years (QALYs) and incurred costs specific to the treatment arm and the health state occupied. A time horizon of 30 years, reflecting a lifetime horizon, was used. The modelled population was based on PAPILLON study participants. A half-cycle correction was applied. The intervention was ACP. Comparators were CP, pembrolizumab-

CP, and pembrolizumab monotherapy. These were presented as a weighted comparator (Physician's Choice of Therapy) in the Applicant base case. Due to uncertainty in the proportions treated with each comparator, individual pairwise comparisons were presented in the NCPE adjusted base case.

The key treatment effects captured by the CEM were the delay of disease progression and death. Kaplan Meier (KM) data from PAPILLON were used to inform efficacy inputs for ACP and CP treatment arms. Parametric models were fitted to the KM data for PFS and OS. For the Applicant base case, the gamma distribution was selected to extrapolate OS in the CP arm. However, the Review Group considered the log-logistic distribution to be more appropriate. For the pembrolizumab-CP and pembrolizumab monotherapy comparators, efficacy inputs were informed by relative treatment effects derived from the ITC. For the Applicant base case, the loglogistic distribution was selected to extrapolate OS in the pembrolizumab-CP arm. However, the Review Group considered the lognormal distribution to be more appropriate. No adjustments were made to the pembrolizumab-monotherapy arm, as the Review Group considered the outcomes of the ITC to be highly uncertain. Long-term extrapolations of OS for both the intervention and comparators were highly uncertain.

The Applicant modelled time-on-treatment for ACP and CP using time to treatment discontinuation or death (TTDD) KM data from the PAPILLON study. Time-on-treatment for pembrolizumab-CP and pembrolizumab monotherapy were modelled using time to next treatment data from the ITC. The Applicant chose a Weibull distribution for both the amivantamab and CP components in the ACP arm. However, the Review Group considered the gamma distribution to be a more appropriate choice.

An SLR was conducted to identify HRQoL evidence for patients with advanced NSCLC with EGFR exon20ins. Utility values used in the CEM were derived from PAPILLON. Limitations included a high proportion of missing observations and the open-label design of PAPILLON. Baseline utilities in the CEM were higher than in other HTA submissions, to the NCPE, for drugs for NSCLC; this may have biased results in favour of the intervention.

Costs and resources included were drug acquisition costs, drug administration costs, subsequent treatment costs, AE costs and disease management costs. A once-off, end-of-life cost was also included.

Results

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

Table 1: Applicant incremental cost-effectiveness results (pairwise comparisons)[a,b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Base case[c]					
ACP	175,801	2.80	-	-	-
PCT[d]	66,384	1.51	109,418	1.29	85,105
Scenario analyses[e]					
ACP	175,801	2.80	-	-	-
CP	46,646	1.48	129,156	1.32	98,077
Pembrolizumab-CP	108,168	1.57	67,633	1.23	54,844
Pembrolizumab	75,695	1.55	100,106	1.25	80,193

ACP: amivantamab in combination with carboplatin and pemetrexed; CIC: commercial-in-confidence; CP: carboplatin in combination with pemetrexed; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; PCT: Physician's choice of treatment; pembrolizumab-CP: pembrolizumab in combination with carboplatin and pemetrexed; QALY: quality adjusted life year.

a   A CIC PAS has been offered for amivantamab, and is in place for pembrolizumab, which have not been included in this Table.
b   Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% was applied to costs and outcomes.
c   Corresponding probabilistic ICER using 1,000 iterations = €83,397/QALY.
d   PCT comprised CP (60%), pembrolizumab-CP (25%) and pembrolizumab alone (15%). Distribution of comparators was informed by clinical opinion to the Applicant.
e   Corresponding probabilistic ICER using 1,000 iterations for (i) CP comparison = €95,994/QALY, (ii) for pembrolizumab-CP comparison = €53,191/QALY, (iii) for pembrolizumab monotherapy comparison = €79,348/QALY.

An NCPE adjusted base case was presented for the comparisons of ACP versus CP, and ACP versus pembrolizumab-CP. An NCPE adjusted base case was not conducted for the comparison of ACP versus pembrolizumab monotherapy. The outputs from the ITC informing treatment effectiveness, versus pembrolizumab monotherapy, were considered to be too uncertain.

Several changes were made to inform the NCPE adjusted base case. For both comparisons, the distribution used to extrapolate TTDD for the amivantamab and CP components of ACP were changed from Weibull to gamma. For ACP versus CP, the loglogistic distribution was used instead of the gamma distribution to extrapolate OS in the CP arm. For ACP versus pembrolizumab-CP, the truncated ATT estimand was used (rather than the untruncated); and the lognormal distribution was used instead of loglogistic to extrapolate OS in the pembrolizumab-CP arm. Results of the NCPE adjusted base case are presented in Table 2.

Table 2: NCPE adjusted base case incremental cost-effectiveness results (pairwise comparisons)[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
ACP versus CP					
ACP	181,850	2.80	-	-	-

CP	48,401	1.65	133,449	1.15	115,842
ACP versus pembrolizumab-CP					
ACP	181,850	2.80	-	-	-
Pembrolizumab-CP	110,637	2.12	71,213	0.68	104,295

ACP: amivantamab in combination with carboplatin and pemetrexed; CIC: commercial-in-confidence; CP: carboplatin in combination with pemetrexed; ICER: incremental cost-effectiveness ratio; NCPE: National Centre for Pharmacoeconomics; PAS: patient access scheme; pembrolizumab-CP: pembrolizumab in combination with carboplatin and pemetrexed; QALY: quality adjusted life year

a A CIC PAS has been offered for amivantamab, and is in place for pembrolizumab, which have not been included in this Table.
b Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% was applied to costs and outcomes.
c Corresponding probabilistic ICER using 1,000 iterations for (i) CP comparison = €113,868/QALY, (ii) for pembrolizumab-CP comparison = €98,091/QALY.

Sensitivity analysis

Cost-effectiveness results for ACP versus pembrolizumab-CP were highly sensitive to the choice of estimand used in the ITC. Using the ATE estimand increased the NCPE adjusted base case incremental cost-effectiveness ratio (ICER) to €179,164 per QALY.

Under NCPE adjusted base case assumptions, the probability of cost-effectiveness of ACP versus CP at the willingness-to-pay thresholds of €45,000 per QALY and €20,000 per QALY was 0.3% and 0%, respectively. The probability of cost-effectiveness of ACP versus pembrolizumab-CP at these thresholds was 10.5% and 0.8%, respectively.

A price-ICER analysis, using NCPE adjusted base case assumptions, indicated that reductions of 72.2% and 94.5% on the price to wholesaler of amivantamab would be required for ACP to demonstrate cost-effectiveness versus CP at the willingness-to-pay thresholds of €45,000 per QALY and €20,000 per QALY, respectively. For the same analysis of ACP versus pembrolizumab-CP, respective reductions of 40.3% and 53.6% would be required.

4. Budget impact of amivantamab

The price to wholesaler for one vial of amivantamab 350mg per 7ml concentrate for solution for infusion is €1,217.50. The cost per patient per treatment course of ACP is highly variable and sensitive to assumptions regarding time on treatment. Applicant and NCPE estimates of cost per patient per treatment course of ACP (incorporating Framework Agreement rebate (9%), and VAT) were €164,036 and €210,508, respectively. The difference in cost estimates was due to different assumptions regarding time on treatment (Applicant 57.92 weeks; NCPE 75.7 weeks).

The Applicant predicted that 11 patients will be treated with ACP each year, from Year One through to Year Five. Using the Review Group's preferred assumptions, the cumulative five-

year gross drug budget impact of ACP was estimated to be €10.9 million including VAT. The cumulative five-year net drug budget impact was estimated to be €8.3 million including VAT. Budget impact estimates were very sensitive to estimated patient numbers, which were highly uncertain.

5. Patient Organisation Submission

A patient organisation submission was received from the Irish Lung Cancer Community and has been shared with the HSE. This submission will form part of the data that the HSE considers when making their drug-funding decision.

6. Conclusion

The NCPE recommends that amivantamab, in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced NSCLC with activating epidermal EGFR exon20ins mutations, should not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments.

Next steps: The NCPE Assessment Report and recommendation, will be considered by the HSE when making their decision on reimbursement, while also having regard to the Patient Organisation Submission and the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

Further information on this process may be found **here.**