NCPE Assessment

Summary

Amivantamab in combination with lazertinib (Rybrevant® in combination with Lazcluze®)

HTA ID: 25006

27 May 2026

Applicant: Johnson and Johnson Innovative Medicine

Amivantamab in combination with lazertinib for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of amivantamab (Rybrevant®) in combination with lazertinib (Lazcluze®) for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with EGFR exon 19 deletions or exon 21 L858R substitution mutations.

Following assessment of the Applicant's submission, the NCPE recommends that amivantamab in combination with lazertinib not be considered for reimbursement 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 solution for intravenous infusion in combination with lazertinib. The Applicant is the marketing authorisation holder for both medicines. 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 August 2025, Johnson and Johnson Innovative Medicine submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of amivantamab (Rybrevant®) solution for intravenous infusion in combination with lazertinib (Lazcluze®) for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with EGFR exon 19 deletions or exon 21 L858R substitution mutations. Johnson and Johnson Innovative Medicine is seeking reimbursement of amivantamab on the Oncology Drug Management System and reimbursement of lazertinib on the High Tech Arrangement.

Amivantamab is a fully human, bispecific antibody that targets EGFR and mesenchymal–epithelial transition (MET) mutations. It is administered by intravenous infusion; dosing is weight based. A formulation of amivantamab for administration by subcutaneous injection has also, more recently, received European marketing authorisation approval; however, this was not the focus of this assessment. Lazertinib is an irreversible EGFR tyrosine kinase inhibitor. It is administered orally at a dose of 240mg once daily. Both drugs are continued until disease progression or unacceptable toxicity.

In Ireland, osimertinib monotherapy is predominantly prescribed first-line to treat adults with advanced NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations. Osimertinib was included as the only comparator of interest in this submission, which the Review Group considered appropriate.

1. Comparative effectiveness of amivantamab in combination with lazertinib

The efficacy and safety of amivantamab in combination with lazertinib (amivantamab + lazertinib) was informed by MARIPOSA, which is an ongoing phase III, randomised, active-controlled trial. Eligible participants were adults with untreated EGFR-mutated (exon 19 deletion or exon 21 L858R substitution), locally advanced or metastatic NSCLC. Participants were randomised to receive treatment with amivantamab + lazertinib (n=429), osimertinib (n=429) or lazertinib (n=216). The lazertinib arm was included only to assess the contribution of amivantamab to amivantamab + lazertinib. Comparative efficacy estimates of lazertinib versus the other two arms were not pre-specified endpoints. Results of these comparisons

were not considered further. 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. Study completion is anticipated late 2027.

Baseline demographic and clinical characteristics of the MARIPOSA population were balanced between treatment arms. The median age was 63 years; 61.6% were female, 58.6% were Asian and 38.0% were White. All participants harboured either an exon 19 deletion (60.1%) or an exon 21 L858R substitution mutation (39.9%).

At the first interim analysis (11 August 2023), with a median follow-up of 22.01 months, a statistically significant improvement in PFS of 7.1 months was observed in favour of amivantamab + lazertinib compared to osimertinib (hazard ratio (HR) 0.70, 95% confidence interval (CI) 0.58 to 0.85). Median PFS was 23.7 months (95% CI 19.1 to 27.7) and 16.6 months (95% CI 14.8 to 18.5) for the amivantamab + lazertinib arm and osimertinib arm, respectively. At the final OS analysis (04 December 2024), with a median follow-up of 37.8 months, amivantamab + lazertinib demonstrated a statistically significant improvement in OS compared to osimertinib (HR 0.75, 95% CI 0.61 to 0.92). Median OS was not evaluable (95% CI 42.9 months to not evaluable) in the amivantamab + lazertinib arm; it was 36.7 months (95% CI 33.4 to 41.0) in the osimertinib arm. OS data remained immature. A considerable proportion of participants were censored for both PFS and OS (approximately 48% and 55%, respectively) in both study arms. Long-term comparative effectiveness of amivantamab + lazertinib versus osimertinib on PFS and OS beyond trial follow-up is unknown. HRQoL outcomes were comparable between treatment arms. Patients' baseline physical functioning and global health status were maintained in both treatment arms, with participants in both arms reporting slight overall improvements. The low symptom burden observed at baseline was also maintained in both treatment arms. The open-label nature of MARIPOSA may also have been a potential source of bias, particularly with regard to patient reported outcomes.

2. Safety of amivantamab in combination with lazertinib

The safety of amivantamab + lazertinib for this indication was informed by the safety analysis set for the MARIPSOA trial at the December 2024 final OS analysis (amivantamab + lazertinib arm n=421; osimertinib arm n=428). Almost all participants experienced one or more treatment emergent adverse events (TEAEs) (100% in the amivantamab + lazertinib arm, versus 99.5% in the osimertinib arm, respectively). The incidence of grade ≥ 3 TEAEs was considerably higher in the amivantamab + lazertinib arm (80.0%) compared with the osimertinib arm (52.3%), as was the incidence of serious adverse events (55.3% versus 41.4%, respectively). The most commonly reported grade ≥ 3 TEAEs included rash (17.3% versus 0.7%, respectively), and paronychia (11.6% versus 0.5% respectively).

Special warnings for amivantamab include infusion related-reactions (IRRs), skin and nail reactions, eye disorders, interstitial lung disease (ILD), and, when co-administered with lazertinib, venous thromboembolism (VTE). Antihistamines, antipyretics and glucocorticoids are recommended prior to administration of amivantamab to reduce the risk of IRRs. Prophylactic anticoagulants should be administered to prevent occurrence of VTE. Patients should also be monitored for VTEs, ILD or ILD-like adverse reactions. If symptoms develop, amivantamab + lazertinib treatment should be interrupted, pending investigation. If ILD or ILD-like adverse reactions are confirmed, treatment should be permanently discontinued. Similarly, if patients present with a severe rash without improvement within two weeks following amivantamab + lazertinib, treatment should be interrupted pending investigation.

3. Cost effectiveness of amivantamab in combination with lazertinib

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 MARIPOSA 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 MARIPOSA study participants. A half-cycle correction was applied. The intervention was amivantamab + lazertinib; the comparator was

osimertinib.

The key treatment effects captured by the CEM were the delay of disease progression and death. Kaplan Meier (KM) data from MARIPOSA were used to inform efficacy inputs for amivantamab + lazertinib and osimertinib treatment arms. Parametric models were fitted to the KM data for PFS and OS. For the Applicant base case, the Weibull distribution was selected to extrapolate OS in the osimertinib arm. However, the Review Group considered the gamma distribution provided similar model fit and generated plausible OS estimates that were more optimistic but which also aligned with clinical opinion and published evidence. Long-term extrapolations of OS for both the intervention and comparators were generally considered to be highly uncertain. The Applicant modelled time-on-treatment for amivantamab + lazertinib using time to treatment discontinuation (TTD) KM data from the MARIPOSA study. The Applicant chose an exponential distribution for both the amivantamab and lazertinib components. However, the choice of exponential implied a hazard rate that remained constant over time, which the Review Group did not consider was reflected by data from MARIPOSA. The Weibull distribution generated TTD estimates similar to those predicted by the exponential, and which the Review Group considered to better align with clinical opinion.

A systematic literature search was conducted to identify HRQoL evidence for patients with advanced NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations. Utility values used in the CEM were derived from MARIPOSA. Baseline utilities in the CEM were higher than in other HTA submissions for drugs for NSCLC; this may have biased results in favour of amivantamab + lazertinib.

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

Results

Deterministic incremental cost-effectiveness ratios (ICERs) for amivantamab + lazertinib versus osimertinib, generated under Applicant base case and NCPE adjusted base case assumptions, are presented in Table 1 and Table 2, respectively.

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

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Base case					
Osimertinib[d]	176,361	2.56	-	-	
Amivantamab + lazertinib	397,914	3.42	221,553	0.86	257,841

Amivantamab + lazertinib: amivantamab in combination with lazertinib; **ICER:** incremental cost-effectiveness ratio; **QALY:** quality-adjusted life year

a Corresponding probabilistic ICER using 1,000 iterations = €260,285 per QALY.
b Discount rate of 4% was applied to costs and outcomes.
c Figures in the table are rounded, and so calculations may not be directly replicable.
d A commercial in confidence patient access scheme is in place for osimertinib, which is not included in these results.

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

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Base case					
Osimertinib[d]	177,184	2.71	-	-	-
Amivantamab + lazertinib	406,122	3.42	228,938	0.72	319,429

Amivantamab + lazertinib: amivantamab in combination with lazertinib; **ICER:** incremental cost-effectiveness ratio; **NCPE:** National Centre for Pharmacoeconomics; **QALY:** quality-adjusted life year

a Corresponding probabilistic ICER using 1,000 iterations = €322,018 per QALY.
b Discount rate of 4% was applied to costs and outcomes.
c Figures in the table are rounded, and so calculations may not be directly replicable.
d A commercial in confidence patient access scheme is in place for osimertinib, which is not included in these results.

Several changes were made to inform the NCPE adjusted base case. The distribution used to extrapolate TTD for the amivantamab and lazertinib components was changed from exponential to Weibull. The distribution used to extrapolate OS for the osimertinib arm was changed from Weibull to gamma.

Sensitivity analysis

Cost-effectiveness results were most sensitive to assumptions related to extrapolation of OS for both amivantamab + lazertinib and osimertinib, and extrapolation of TTD for amivantamab + lazertinib. Although not the focus of the assessment, modelling the subcutaneous formulation of amivantamab instead of the intravenous formulation, was not identified as being a key driver of cost-effectiveness results. Under NCPE adjusted base case assumptions, the probability of cost-effectiveness of amivantamab + lazertinib versus osimertinib at the willingness-to-pay thresholds of €45,000 per QALY and €20,000 per QALY was 0% in both cases.

A price-ICER analysis, using NCPE adjusted base case assumptions, indicated that, where a rebate was applied to only one component of the regimen, there was no rebate of sufficient magnitude such that cost-effectiveness of amivantamab + lazertinib could be demonstrated.

Price reductions would have to be applied to both amivantamab and lazertinib in order for amivantamab + lazertinib to demonstrate cost-effectiveness versus osimertinib. A rebate of 61.3% (inclusive of the Framework Agreement rebate) on the prices to wholesaler of both amivantamab and lazertinib would be required for amivantamab + lazertinib to demonstrate cost-effectiveness versus osimertinib at the willingness-to-pay threshold of €45,000 per QALY. A rebate of 66.1% on the prices to wholesaler of both would be required for amivantamab + lazertinib to demonstrate cost-effectiveness versus osimertinib at the willingness-to-pay threshold of €20,000 per QALY.

4. Budget impact of amivantamab in combination with lazertinib

The price to wholesaler for one vial of amivantamab 350mg per 7ml concentrate for solution for infusion is €1,217.50. The price to wholesaler for one pack of lazertinib 240mg oral tablets (28 tablets per pack) and 80mg oral tablets (56 tablets per pack) is €7,384.15 and €4,922.77, respectively. The estimated cost per patient per treatment course of amivantamab + lazertinib is €449,504 (including VAT), inclusive of Framework Agreement rebate, pharmacy fees and IV administration costs. Costs were informed by time on treatment data from MARIPOSA and considered dose skipping and dose reductions. It is uncertain if these data from MARIPOSA would be representative of what might be observed in Irish clinical practice if amivantamab + lazertinib were reimbursed.

The Applicant predicted that 19 patients would be treated with amivantamab + lazertinib in Year One, rising to 32 patients in Year Five. Using the Review Group's preferred assumptions for time-on-treatment, the cumulative five-year gross drug budget impact of amivantamab + lazertinib was estimated to be €48.05 million including VAT. The cumulative five-year net drug budget impact was estimated to be €29.64 million including VAT. Budget impact estimates were sensitive to patient numbers, which were very uncertain.

5. Patient Organisation Submission

A patient organisation submission was received from the Irish Lung Cancer Community. This submission will form part of the information that the HSE considers when making their drug funding decision.

6. Conclusion

The NCPE recommends that amivantamab in combination with lazertinib for the first-line treatment of adult patients with advanced NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments*.

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

Further information on this process may be found here.