# NCPE Technical Summary

## Nirmatrelvir+Ritonavir (Paxlovid®)

## HTA ID: 22014

June 2024

Applicant: Pfizer Healthcare Ireland

The cost-effectiveness of nirmatrelvir + ritonavir for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of nirmatrelvir + ritonavir (Paxlovid®). Following assessment of the Applicant's submission, the NCPE recommends that nirmatrelvir + ritonavir (Paxlovid®) be considered for reimbursement if cost-effectiveness can be improved*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Pfizer Healthcare Ireland) Health Technology Assessment of nirmatrelvir + ritonavir (Paxlovid®). 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.

## Summary

In February 2024, Pfizer Healthcare Ireland submitted a dossier which investigated the clinical effectiveness, cost-effectiveness and budget impact of nirmatrelvir + ritonavir for the treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19. Reimbursement is sought under the Community Drugs Schemes.

Although COVID-19 is primarily a disease of the respiratory system affecting lung parenchyma with associated fever, cough and breathlessness as the predominant symptoms, multiple organ systems may be involved including the liver, brain, kidneys and the intestine. COVID-19 may infect all age groups and is transmitted via direct contact or respiratory droplets generated during coughing or sneezing by the infected patient. The World Health Organisation declared COVID-19 a pandemic on March 11th 2020 and the challenge in restraining COVID-19 was compounded by the emergence of several variants of SARS-CoV-2.

Vaccination is the primary intervention against COVID-19 and the initial vaccination programme had an uptake of approximately 89% in persons 12 years and older and the first booster programme in November 2021 had an uptake exceeding 97% in those aged 65 years or more. The spectrum of illness associated with acute COVID-19 ranges from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome. The Omicron variant is associated with less likelihood of severe symptoms relative to prior COVID-19 variants. Older persons and those who have certain underlying conditions, including cardiovascular disease, obesity and diabetes are at increased risk for severe outcomes from COVID-19 infection.

Nirmatrelvir + ritonavir (Paxlovid) is indicated for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19. Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro), also known as 3C-like protease (3CLpro). Nirmatrelvir and ritonavir are substrates for cytochrome P450 3A4 (CYP 3A4) and ritonavir is also a potent inhibitor of this isoenzyme, thereby increasing nirmatrelvir concentrations when co-administered in Paxlovid. The recommended dosage is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally every 12 hours for 5 days. Paxlovid should be administered as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset. Paxlovid is compared to best standard of care (e.g antipyretics) in this economic evaluation.

## 1. Comparative effectiveness of nirmatrelvir + ritonavir (Paxlovid®)

The clinical evidence for the use of nirmatrelvir + ritonavir for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19 was primarily derived from the EPIC-HR trial. In addition, real world evidence was provided to support the generalisability of the EPIC-HR trial data.

The EPIC-HR study was a phase 2-3 double-blind, randomised, controlled trial in which symptomatic, unvaccinated, non-hospitalised adults at high risk for progression to severe COVID-19 were assigned in a 1:1 ratio to receive either 300 mg nirmatrelvir + 100 mg ritonavir or placebo every 12 hours for 5 days. Eligible patients were required to be at least 18 years, to have confirmed SARS-CoV-2 infection and symptom onset no more than 5 days before randomisation, with at least one sign or symptom of COVID-19 on the day of randomisation and to have at least one characteristic or coexisting condition associated with high risk of progression to severe COVID-19. Key exclusion criteria were previous confirmed SARS-CoV-2 infection or hospitalisation for COVID-19, anticipated need for hospitalisation within 48 hours after randomisation and prior receipt of convalescent COVID-19 plasma or SARS-CoV-2 vaccine. A total of 2246 patients underwent randomisation; 1120 patients received nirmatrelvir + ritonavir and 1126 received placebo. The median age at randomisation was 46 years and 51.1% of participants were male. The mean time since the first symptom was 2.96 days. The most common pre-specified characteristics and coexisting conditions associated with a risk of progression to severe COVID-19 included a BMI ≥ 25 kg/m² (80.5%), current smoking (39%) and hypertension (32.9%) with 61% having two or more conditions.

In the planned interim analysis of patients treated within 3 days after symptom onset (modified intention-to-treat population, comprising 774 of the 1361 patients in the full analysis population), the incidence of the primary end-point i.e COVID-19 related hospitalisation or death by day 28 was lower in the nirmatrelvir + ritonavir group than in the placebo group by 6.32 percentage points (95% confidence interval [CI], -9.04 to -3.59;P<0.001; relative risk reduction, 89.1%). The incidence was 0.77% (3 of 389 patients, no deaths) in the nirmatrelvir + ritonavir group as compared with 7.01% (27 of 385 patients, 7 deaths) in the placebo group. Efficacy was maintained in the final analysis involving 1379 patients in the modified intention-to-treat population with a difference of -5.81 percentage points (95% CI, -7.78 to -3.84;P<0.001; relative risk reduction 88.9%). All 13 deaths occurred in the placebo group.

The first key secondary analysis was conducted in patients who commenced treatment within 5 days after symptom onset to evaluate hospitalisation for COVID-19 or death from any cause. In the final analysis of this population 8 out of 1039 patients (0.77%) in the nirmatrelvir + ritonavir group and 66 of 1046 (6.31%) in the placebo group were hospitalised for COVID-19 or died from any cause through day 28 (P<0.001) which represented an 87.8% relative risk reduction. The NCPE Review Group note that the study did not collect data beyond the day 35 visit and there was insufficient quality of life data captured by the EQ-5D instrument in EPIC-HR to be used in this economic analysis.

The NCPE Review Group noted that the submitted economic evaluation is based on the EPIC-HR clinical trial results and the assumption that the efficacy of nirmatrelvir + ritonavir (Paxlovid) is the same in a vaccinated population as compared with an unvaccinated population. This assumption is not supported by the EPIC-SR trial which questions the efficacy of Paxlovid in patients who (a) are fully vaccinated and have at least one risk factor for severe COVID-19 or (b) are at standard risk for severe COVID-19.

## 2. Safety of nirmatrelvir + ritonavir (Paxlovid®)

In the EPIC-HR trial the incidence of adverse events that emerged during or after the treatment period was similar among recipients of nirmatrelvir + ritonavir (22.6%) as compared with placebo (23.9%). The most frequently reported adverse events among the active treatment group included dysgeusia (5.6%), diarrhoea (3.1%), increased ALT (1.5%), headache (1.4%), reduced creatinine clearance (1.4%), nausea (1.4%) and vomiting (1.1%). These adverse events were nonserious and resolved. Patients who received nirmatrelvir + ritonavir reported fewer grade 3 or 4 adverse events as compared with the placebo group (4.1% versus 8.3%), fewer serious adverse events (1.6% versus 6.6%) and fewer adverse events leading to discontinuation of treatment (2% versus 4.3%). Through day 34, no serious adverse events resulting in death occurred in the nirmatrelvir + ritonavir group but there were 13 deaths among placebo recipients and all deaths were COVID-19 related. The potential for serious drug-drug interactions is a concern and prescribers are advised to consider a complete list of medications prior to co-prescribing nirmatrelvir + ritonavir. The HSE Medicines Management Programme has advised prescribers that the National Medicines Information Centre (NMIC) is a resource that can be used to enhance safe and effective prescribing.

## 3. Cost effectiveness of nirmatrelvir + ritonavir (Paxlovid®)

### Methods

A Markov model was constructed to calculate lifetime costs and quality adjusted life years (QALYs)

for treatment with nirmatrelvir + ritonavir versus best supportive care (in the form of antipyretic agents). The model comprised of a decision tree component, simulating the first year of COVID-19 infection coupled to a long term horizon Markov model component which allowed estimation of the impact of long-COVID, survival and the long-term impact of mechanical ventilation in the intervention and comparator arms. The population considered in the base case analysis included non-hospitalised, unvaccinated, symptomatic adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. The intervention was nirmatrelvir + ritonavir (Paxlovid) at the recommended dose of 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) taken together orally every 12 hours for 5 days.

Treatment effectiveness was captured via the estimation of the reduction in symptom duration, risk of hospitalisation and the risk of death. Data from the modified intention-to-treat population of the EPIC-HR trial informed effectiveness estimates in the basecase analysis. Healthcare costs included medical consultations, hospitalisation to a general ward, admission to the intensive care unit with or without mechanical ventilation and costs associated with long COVID. Additional costs included drug costs and pharmacy fees.

Patient outcomes were quantified as quality-adjusted life years (QALYs). The EPIC-HR trial did not collect data on the health related quality of life impact of COVID-19. Therefore, utility values from the two independent COVID-19 Health Technology Assessments (HTAs) carried out by the Institute for Clinical and Economic Review and the National Institute for Health and Care Excellence were used in the basecase analysis. A baseline utility (pre-infection) was assigned at the start of the infection period and as patients advance through each of the events in the model a disutility was applied to the baseline utility.

Costs and quality adjusted life-years (QALYs) were discounted at a rate of 4% over the lifetime horizon. Results in the base case represented the perspective of the Health Service Executive (HSE).

### Results

For the treatment of COVID-19 infection in adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 the base-case (deterministic) incremental cost-effectiveness ratio (ICER) for nirmatrelvir + ritonavir versus standard of care (SoC) was estimated at €10,681/QALY. An analysis of costs and QALYs is shown in table 1.

**Table 1. Cost-effectiveness of nirmatrelvir + ritonavir for the treatment of COVID-19 infection versus standard of care (SoC).**

| Treatments | Total costs (€) | Total QALYs | Incremental costs (€) | Incremental QALYs | ICER (€/QALY) |
|---|---|---|---|---|---|
| Nirmatrelvir + Ritonavir | €53,457 | 16.01 | - | - | - |
| Standard of care (SoC) | €52,505 | 15.92 | €952.06 | 0.089 | 10,681 |

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

Figures in the table are rounded, and so calculations may not be directly replicable

### Sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted and the ICER was estimated at €10,689/QALY. The probability of nirmatrelvir + ritonavir being cost-effective was 89% at the €45,000/QALY threshold. A deterministic sensitivity analysis was also presented. The most important parameters that impacted the cost-effectiveness of nirmatrelvir + ritonavir versus best supportive care included the proportion of patients hospitalised in the high risk group, drug cost, treatment efficacy in relation to hospitalisations, mortality on the general ward and proportion of patients with long COVID post-hospitalisation. The basecase ICER did not exceed €13,636/QALY for any of these parameters.

## 4. Budget impact of nirmatrelvir + ritonavir (Paxlovid®)

The cost of a five day course of nirmatrelvir + ritonavir (including pharmacy fees) was €1,015.12. The eligible patient population was estimated at 9,259 per annum. An alternative estimate of patient numbers, based on HSE guidelines was 5,532 per annum. The 5 year gross drug budget impact for nirmatrelvir + ritonavir was estimated at €46,824,210. If the population based on HSE guidelines was used the 5 year gross budget impact was estimated at €27,976,572. The 5-year net drug budget impact under the base case for nirmatrelvir + ritonavir was estimated at €34,411,153. If eligible population estimates aligned to HSE treatment guidelines are used the 5 year net budget impact was calculated at €20,560,008.

## 5. Patient Organisation Submission

There was no patient organisation submission for this Health Technology Assessment.

## 6. Conclusion

The limitations associated with the use of the EPIC-HR data to inform the economic model, the high cost of nirmatrelvir + ritonavir and the significant budget impact are noted. There remains a requirement for safe and effective treatments for COVID-19 and in view of this the NCPE recommends that Paxlovid be considered for reimbursement if cost-effectiveness can be improved*

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