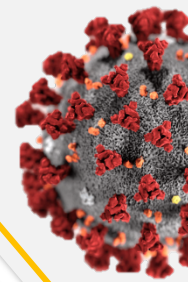




PROTEASE INHIBITORS (PAXLOVID®) – ORAL TREATMENT FOR COVID-19 (updated)



Based on updated available evidence up to 28 December 2021

PURPOSE

To provide scientific evidence on the efficacy/effectiveness, safety and cost-effectiveness of protease inhibitors Paxlovid® for the treatment of Covid-19.

INTRODUCTION

The ongoing unprecedented pandemic of coronavirus disease 2019 (Covid-19) has resulted in over 256 million confirmed cases and over 5.1 million deaths and demands effective treatment against SARS-CoV-2 infection.¹

It is known that the infection of SARS-CoV-2 critically depends on diverse viral or host proteases, which mediate viral entry, viral protein maturation, as well as the pathogenesis of the viral infection.² Protease inhibitors have been proved to be effective toward a variety of viral infections ranging from HIV to influenza virus, suggesting them as a promising antiviral treatment for Covid-19.

Building on their capabilities in developing antiviral protease inhibitors for HIV and hepatitis C, Pfizer commenced research on the revived compound identified in 2003 for treating severe acute respiratory syndrome (SARS) epidemic in China, given the similarities between the structures of the SARS-CoV-1 and the SARS-CoV-2 proteases.³ In preclinical in vitro studies, many of the SARS-CoV-1 protease inhibitors identified in 2003 were found to also inhibit the SARS-CoV-2 protease.³

Paxlovid® and its mechanism of action

Paxlovid® (co-packaged of nirmatrelvir tablets and ritonavir tablets) is a SARS-CoV-2 main protease (Mpro) inhibitor or also known as SARS-CoV-2 3CL protease inhibitor.⁴ Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 Mpro, designed to inhibit viral replication at a stage known as proteolysis, which occurs before viral RNA replication. In preclinical studies, nirmatrelvir did not demonstrate evidence of mutagenic DNA interactions. Ritonavir is an HIV-1 protease inhibitor and is not active against SARS-CoV-2 Mpro. It inhibits the CYP3A-mediated metabolism of nirmatrelvir, thus helps slow the metabolism, or breakdown, of nirmatrelvir in order for it to remain active in the body for longer periods of time at higher concentrations to help combat the virus.

Current variants of concern can be resistant to treatments that inhibit the spike protein found on the surface of the SARS-CoV-2 virus. In contrast, Paxlovid® works intracellularly by binding to the protease of the SARS-CoV-2 virus to inhibit viral replication. Nirmatrelvir has shown in vitro antiviral activity against current variants of concern (i.e., alpha, beta,

delta, gamma, lambda, mu as well as the latest Omicron). However, additional in vitro studies against Omicron are still underway.

As of the time of writing the report, Paxlovid® has yet to be approved, but has received authorisation for emergency use (EUA) by FDA, for the treatment of mild-to-moderate Covid-19 in adults and paediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS CoV-2 viral testing, and who are at high-risk for progression to severe Covid-19, including hospitalisation or death. It is to be administered at a dose of 300 mg (two 150 mg tablets) of nirmatrelvir with one 100 mg tablet of ritonavir, given twice-daily for five days.

SUMMARY OF SCIENTIFIC EVIDENCE

Multiple trials are currently in progress to evaluate two investigational antiviral protease inhibitors developed by Pfizer; orally administered (Paxlovid®) and intravenously administered candidate.³

Evidence on the efficacy and safety of Paxlovid® for the treatment of Covid-19 is limited to an interim analysis of the phase 2/3 study published on the company's website.^{3,4}

Evidence on Efficacy⁴

A phase 2/3 randomised, double-blind trial, EPIC-HR (Evaluation of Protease Inhibition for Covid-19 in High-Risk Patients), evaluated the efficacy and safety of Paxlovid®, co-administered with a low dose of HIV antiviral ritonavir (to help slow down the body's metabolism of Paxlovid®), in unvaccinated non-hospitalised participants with a confirmed diagnosis of SARS-CoV-2 infection who are at high risk of progression to severe illness.³ Patients were randomised (1:1) to receive either a placebo or Paxlovid® in combination with ritonavir, orally every 12 hours for five days. The enrolment in this trial ceased in November 2021 due to efficacy demonstrated in a scheduled interim analysis. At the time of the decision to stop recruiting patients, enrolment was at 70% of the 3,000 planned patients from clinical trial sites across North and South America, Europe, Africa, and Asia, with 45% of patients located in the United States.³

Results from the interim analysis involving 1,219 patients who completed 28 days of follow-up found 89% reduction in Covid-19-related hospitalisation or death from any cause compared to placebo in patients treated within three days of symptom onset (primary endpoint).⁴ Following randomisation, 0.7% of patients who received Paxlovid® were hospitalised through Day 28 (5/697 hospitalised with no deaths), compared to 6.5% of patients who received placebo and were hospitalised or died (44/682 hospitalised with 9 subsequent deaths; $p < 0.0001$). Similar reductions in Covid-19-related hospitalisation or death were observed in patients treated within five days of symptom onset; 0.8% of patients who received Paxlovid® were hospitalised or died through Day 28 following randomisation (8/1039 hospitalised, with no deaths), compared to 6.3% of patients who received a placebo (66/1046 hospitalised with 12 subsequent deaths; $p < 0.0001$). In terms of hospitalisation among patients 65 years of age or older, relative risk reduction was 94%; 1.1% of patients who received treatment were hospitalized through Day 28, compared to 16.3% of patients who received placebo ($p < 0.0001$). In the overall study population through

day 28, no deaths were reported in patients who received Paxlovid® as compared to 12 (1.2%) deaths in patients who received placebo.

In terms of the trial's secondary endpoint, SARS-CoV-2 viral load at baseline and day 5 have been evaluated for 499 patients.⁴ Paxlovid® reduced viral load by approximately 10-fold, or 0.93 log₁₀ copies/mL, relative to placebo, indicating robust activity against SARS-CoV-2 and representing the strongest viral load reduction reported to date for an oral Covid-19 agent.⁴

Ongoing trials

The intravenous (IV) administration of another Pfizer's candidate drug (PF-07304814), has recently completed a Phase 1b study, but no results is retrievable.³ Further study is underway under the National Institutes of Health's (NIH) Accelerating Covid-19 Therapeutic Interventions and Vaccines (ACTIV-3) program to evaluate this treatment option for hospitalised patients with Covid-19.³

Another two clinical trials are currently underway to evaluate protease inhibitors potential use in other groups of patients.³ A phase 2/3 trial, EPIC-SR (Evaluation of Protease Inhibition for Covid-19 in Standard-Risk Patients), in participants with a confirmed diagnosis of SARS-CoV-2 infection who are at standard risk (low risk of hospitalisation or death). Another phase 2/3 EPIC-PEP (Evaluation of Protease Inhibition for Covid-19 in Post-Exposure Prophylaxis) study in adults who live in the same household as an individual with a confirmed symptomatic SARS-CoV-2 infection.³

SAFETY⁴

Analysis of larger cohort of 1881 patients in EPIC-HR trial found comparable safety profile between Paxlovid® (23%) and placebo (24%), most of which were mild in intensity.⁴ Those in the treatment group were less likely to have a serious adverse event (1.6% versus 6.6% in the placebo group) or to have discontinued the study because of an adverse event (2.1% versus 4.2%).

The safety and effectiveness of Paxlovid® have not been established in pregnant, lactating paediatric patients younger than 12 years of age or weighing less than 40kg.

COST

There was no evidence retrieved on cost or cost-effectiveness of Paxlovid®. Company cited cost as USD 250 per 5 days treatment.

CONCLUSION

The retrieved evidence from an interim analysis of a phase 2/3 study showed that Paxlovid® is potentially effective as an oral treatment for unvaccinated non-hospitalised high-risk patients, with acceptable safety profile. However, cost implication of the treatment needs to be further assessed and considered.

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Based on available evidence up to 28 December 2021

Disclosure: The authors of this report has no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia.

Disclaimer: This rapid assessment was prepared to provide urgent evidence-based input during Covid-19 pandemic. The report is prepared based on information available at the time of research and a limited literature. It is not a definitive statement on the safety, effectiveness or cost effectiveness of the health technology covered. Additionally, other relevant scientific findings may have been reported since completion of this report.

**Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health, Malaysia**