Background Summary

# Nirmatrelvir/Ritonavir (PAXLOVID™) for COVID-19

## What is nirmatrelvir/ritonavir (PAXLOVID™)?

Nirmatrelvir/ritonavir (brand name PAXLOVID™) is a protease inhibitor antiviral therapy developed specifically for COVID-19 by Pfizer [1]. Nirmatrelvir (PF-07321332) works to block SARS-CoV-2 3CL protease activity, while a low dose of ritonavir works to slow the breakdown of nirmatrelvir in the body, allowing it to remain active and at a higher concentration for longer.

The separate nirmatrelvir and ritonavir tablets are co-packaged for oral use and are taken together (two tablets of nirmatrelvir and one tablet of ritonavir), twice daily for 5 days [2]. PAXLOVID™ is the first COVID-19 therapy that can be taken at home.

## New in this update (March 29, 2022)

Since the last background summary on nirmatrelvir/ritonavir (PAXLOVID™) was completed (February 22th, 2022),

- Pfizer announced they will be initiating EPIC-PEDS 2/3 study trial of oral Pfizer's PAXLOVID™ in non-hospitalized, symptomatic, pediatric participants with a confirmed diagnosis of COVID-19 who are at risk of progression to severe disease [11].

## Drug approval

### Canada

Health Canada granted authorization for PAXLOVID™ as a COVID-19 treatment on January 17, 2022 [2]. The drug is authorized for adults (18 years+) with mild-to-moderate COVID-19 who are at increased risk of progressing to severe disease, including hospitalization or death. PAXLOVID™ should be used as soon as possible following the diagnosis of COVID-19 and within 5 days of symptom onset.

### US

The US Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for PAXLOVID™ on December 22, 2021 [3]. The EUA is for mild-to-moderate COVID-19 in adults and children (aged 12+ and weighing at least 40 kg) with a confirmed case of COVID-19 and who are at risk of progressing to severe disease, including hospitalization or death.

### Europe

On December 31, 2021, the UK Medicines and Healthcare products Regulatory Agency (MHRA) granted regulatory approval to PAXLOVID™ as a treatment for mild-to-moderate COVID-19 in high-risk individuals [4].

The European Medicines Agency (EMA) issued advice on the use of PAXLOVID™, stating that it can be used to treat adults with COVID-19 who do not require supplemental oxygen and who are at high risk of progressing to severe disease [5]. Treatment with PAXLOVID™ should be administered as soon as possible after the diagnosis of COVID-19 and within 5 days of symptom onset.

The EMA is also evaluating PAXLOVID™ for conditional marketing authorization [6]. On January 27, 2022, the EMA Committee for Medicinal Products for Human Use (CHMP) provided a positive opinion recommending the conditional marketing authorization (CMA) of Pfizer's oral therapy for Covid-19, Paxlovid.[10]

### Australia

On January 20, 2022, The Australian Therapeutic Goods Administration (TGA) provisionally approved the use of Pfizer's Paxlovid (nirmatrelvir and ritonavir) for the treatment of adults with COVID-19 who do not require initiation of oxygen and who are at increased risk of progression to hospitalization or death [9].

## Clinical trials

Epistemonikos lists 13 reports of RCTs on nirmatrelvir for COVID-19, of which 5 are reporting data.

There are multiple ongoing EPIC (Evaluation of Protease Inhibition for COVID-19) trials:

- EPIC-HR (in High-Risk Patients), phase 2/3 (NCT04960202)
- EPIC-SR (in Standard-Risk Patients), phase 2/3 (NCT05011513)
- EPIC-PEP (in Post-Exposure Prophylaxis), phase 2/3 (NCT05047601)

Pfizer announced March 09, 2022 that they will be initiating "EPIC-PEDS", phase 2/3 (NCT05261139) trial in non-hospitalized, symptomatic, pediatric participants with confirmed COVID-19 with risk of progression to severe disease [11].

### EPIC-HR

Publication in *the New England Journal of Medicine*, Hammond et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19 - Feb 16, 2022 [8]

**Summary**

- A phase 2–3 double-blind, randomized, controlled trial
- The aim was to evaluate the effect of timing of remdesivir initiation on patient's clinical outcomes
- Patients were randomly assigned (1:1) to receive PAXLOVID™ (300 mg of nirmatrelvir plus 100 mg of ritonavir) or placebo orally every 12 hours for 5 days.
- 2246 symptomatic, unvaccinated, nonhospitalized adults at high risk for progression to severe COVID-19 were randomized to the following cohorts; nirmatrelvir plus ritonavir (n=1120) or placebo (n=1126)
- Primary outcome: Covid-19–related hospitalization or death from any cause through day 28
- Secondary outcomes: Viral load, and safety
- Results: " The incidence of Covid-19–related hospitalization or death by day 28 was lower in the nirmatrelvir 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%). All 13 deaths occurred in the placebo group. The viral load was lower with nirmaltrelvir plus ritonavir than with placebo at day 5 of treatment, with an adjusted mean difference of −0.868 log10 copies per milliliter when treatment was initiated within 3 days after the onset of symptoms. The incidence of adverse events that emerged during the treatment period was similar in the two groups (any adverse event, 22.6% with nirmatrelvir plus ritonavir vs. 23.9% with placebo; serious adverse events, 1.6% vs. 6.6%; and adverse events leading to discontinuation of the drugs or placebo, 2.1% vs. 4.2%). Dysgeusia (5.6% vs. 0.3%) and diarrhea (3.1% vs. 1.6%) occurred more frequently with nirmatrelvir plus ritonavir than with placebo"

**Conclusions**

- **" Treatment of symptomatic Covid-19 with nirmatrelvir plus ritonavir resulted in a risk of progression to severe Covid-19 that was 89% lower than the risk with placebo, without evident safety concerns."**

### EPIC-SR

The results from an interim analysis of the EPIC-SR study were also announced in Pfizer's December 14, 2021 press release: "Interim analyses of an ongoing second study in standard-risk adults (EPIC-SR) showed a 70% reduction in hospitalization and no deaths in the treated population, compared to placebo, in the secondary endpoint; the novel primary endpoint of self-reported, sustained alleviation of all symptoms for four consecutive days, as compared to placebo, was not met. The study continues." [7]

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***Please note: This summary reflects evidence up to and including March 29, 2022 only.***

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## Search Methods

Date searched: 2022-03-29

- Google for news items and clinical trials in progress
- Epistemonikos L-OVE on COVID-19 (manual search)
- Ovid MEDLINE search with built-in COVID-19 filter: (PF-07321332 or nirmatrelvir or ritonavir or paxlovid).ti,ab.

## References


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***March 29, 2022***