Nirmatrelvir is an oral protease inhibitor that is active against M\textsubscript{PRO}, a viral protease that plays an essential role in viral replication by cleaving the 2 viral polyproteins.\textsuperscript{1} It has demonstrated antiviral activity against all coronaviruses that are known to infect humans.\textsuperscript{2} Nirmatrelvir is packaged with ritonavir (as Paxlovid), a strong cytochrome P450 (CYP) 3A4 inhibitor and pharmacokinetic boosting agent that has been used to boost HIV protease inhibitors. Coadministration of ritonavir is required to increase nirmatrelvir concentrations to the target therapeutic range. The Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for ritonavir-boosted nirmatrelvir on December 22, 2021, for the treatment of COVID-19.\textsuperscript{3}

**Recommendations**

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using nirmatrelvir 300 mg with ritonavir 100 mg (Paxlovid) orally (PO) twice daily for 5 days in nonhospitalized adults (AIIa) and pediatric patients aged ≥12 years and weighing ≥40 kg (BIII) with mild to moderate COVID-19 who are at high risk of disease progression.\textsuperscript{4} Treatment should be initiated as soon as possible and within 5 days of symptom onset.

- For recommendations and a discussion on using ritonavir-boosted nirmatrelvir in nonhospitalized children with COVID-19, see [Therapeutic Management of Nonhospitalized Children With COVID-19](https://www.covid19treatmentguidelines.nih.gov/).

- Ritonavir-boosted nirmatrelvir may be used in patients who are hospitalized for a diagnosis other than COVID-19, provided they have mild to moderate COVID-19, are at high risk of progressing to severe disease, and are within 5 days of symptom onset.

Ritonavir-boosted nirmatrelvir has significant drug-drug interactions, primarily due to the ritonavir component of the combination. Before prescribing ritonavir-boosted nirmatrelvir, clinicians should carefully review the patient's concomitant medications, including over-the-counter medications, herbal supplements, and recreational drugs, to evaluate potential drug-drug interactions.

The following resources provide information on identifying and managing drug-drug interactions.

- Quick reference lists:
  - [Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications](https://www.covid19treatmentguidelines.nih.gov/). Box 1 lists select outpatient medications that are not expected to have clinically relevant interactions with ritonavir-boosted nirmatrelvir, and Box 2 lists select outpatient medications that have clinically relevant drug-drug interactions with ritonavir-boosted nirmatrelvir.

- Web-based drug-drug interaction checker:
  - [The Liverpool COVID-19 Drug Interactions website](https://www.covid19treatmentguidelines.nih.gov/)

- Tables with guidance on managing specific drug-drug interactions:
  - The [Ontario COVID-19 Science Advisory Table](https://www.covid19treatmentguidelines.nih.gov/)
  - The FDA EUA [fact sheet](https://www.covid19treatmentguidelines.nih.gov/) and [checklist](https://www.covid19treatmentguidelines.nih.gov/) for ritonavir-boosted nirmatrelvir

For the Panel’s recommendations on preferred and alternative antiviral therapies for outpatients with COVID-19, see [Therapeutic Management of Nonhospitalized Adults With COVID-19](https://www.covid19treatmentguidelines.nih.gov/).
Rationale

The EPIC-HR trial enrolled nonhospitalized adults with mild to moderate COVID-19 who were not vaccinated and who were at high risk of progressing to severe disease. The trial demonstrated that starting ritonavir-boosted nirmatrelvir within 5 days of symptom onset in these patients reduced the risk of hospitalization or death through Day 28 by 89% compared to placebo. This efficacy is comparable to remdesivir (87% relative reduction) and greater than the efficacy reported for molnupiravir (31% relative reduction). However, these agents have not been directly compared in clinical trials.

Although ritonavir-boosted nirmatrelvir demonstrated a clinical benefit during the EPIC-HR trial, the benefits in unvaccinated patients who are at low risk of progression to severe disease or in vaccinated people who are at high risk for progression to severe disease are unclear. The EPIC-SR trial, which included both of these populations, found that ritonavir-boosted nirmatrelvir did not reduce the duration of symptoms and did not have a statistically significant effect on the risk of hospitalization or death compared to placebo, although the event rates were low. Some observational studies have evaluated the effect of ritonavir-boosted nirmatrelvir in vaccinated individuals who are at high risk of progression to severe COVID-19, but because of the limitations of observational studies, these data are not definitive. For information on treatment considerations for vaccinated individuals, see Therapeutic Management of Nonhospitalized Adults With COVID-19.

Because of the potential for significant drug-drug interactions with concomitant medications, this regimen may not be the optimal choice for all patients (see Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir [Paxlovid] and Concomitant Medications).

Ritonavir-boosted nirmatrelvir is expected to be active against the Omicron variant and its subvariants, although there is currently a lack of data on the clinical efficacy of ritonavir-boosted nirmatrelvir against these variants.

Clinical Data

The EPIC-HR study was a multinational randomized trial that compared ritonavir-boosted nirmatrelvir PO twice daily for 5 days to placebo in nonhospitalized patients aged ≥18 years with mild to moderate COVID-19 who were at high risk of clinical progression. Eligible patients were randomized within 5 days of symptom onset, were unvaccinated against COVID-19, and had at least 1 risk factor for progression to severe disease. Patients were excluded if they used medications that were either highly dependent upon CYP3A4 for clearance or strong inducers of CYP3A4.

A total of 2,246 patients enrolled in the trial. The mean age was 46 years, 51% of the patients were men, and 72% were White. Forty-seven percent of the patients tested negative for SARS-CoV-2 antibodies, and 66% started study treatment within 3 days of symptom onset.

Patients who were randomized within 3 days of symptom onset (n = 1,379) were included in the modified intention-to-treat (mITT) analysis. COVID-19-related hospitalizations or all-cause deaths occurred by Day 28 in 5 of 697 patients (0.72%) in the ritonavir-boosted nirmatrelvir arm and in 44 of 682 patients (6.5%) in the placebo arm. Among the 2,085 patients who were randomized within 5 days of symptom onset (mITT1 analysis), COVID-19-related hospitalizations and all-cause deaths occurred in 8 of 1,039 patients (0.77%) in the ritonavir-boosted nirmatrelvir arm and in 66 of 1,046 patients (6.3%) in the placebo arm (89% relative risk reduction; 5.6% estimated absolute reduction; 95% CI, 7.2% to 4.0%; P < 0.001). There were no deaths in the ritonavir-boosted nirmatrelvir arm and 13 deaths in the placebo arm.

A total of 2,224 patients who received at least 1 dose of either ritonavir-boosted nirmatrelvir or placebo were included in the EPIC-HR safety analysis set. Among these patients, dysgeusia and diarrhea occurred more frequently in ritonavir-boosted nirmatrelvir recipients than in placebo recipients (6% vs.
Fewer ritonavir-boosted nirmatrelvir recipients discontinued the study drug due to an adverse event than placebo recipients (2% vs. 4%).

Additional Considerations

• Nirmatrelvir must be administered with ritonavir to achieve sufficient therapeutic plasma concentrations.
• Patients should complete the 5-day treatment course of ritonavir-boosted nirmatrelvir because there are concerns that a shorter treatment course may be less effective or lead to resistance.
• If a patient requires hospitalization after starting treatment, the full 5-day treatment course of ritonavir-boosted nirmatrelvir should be completed unless there are drug-drug interactions that preclude its use.
• There are no data on using combinations of antiviral therapies or combinations of antiviral agents and anti-SARS-CoV-2 monoclonal antibodies for the treatment of nonhospitalized patients with COVID-19. Clinical trials are needed to determine whether combination therapy has a role in the treatment of COVID-19.

Viral Rebound and Symptom Recurrence

• Observational studies and results from the EPIC-HR trial have described SARS-CoV-2 viral rebound and the recurrence of COVID-19 symptoms in some patients who have completed treatment with ritonavir-boosted nirmatrelvir. The frequency, mechanism, and clinical implications of these events are unclear.
• Viral rebound and the recurrence of COVID-19 symptoms can also occur in the absence of treatment with ritonavir-boosted nirmatrelvir.
• The EPIC-HR trial demonstrated a clinical benefit of ritonavir-boosted nirmatrelvir in patients who were not vaccinated and who were at high risk of progressing to severe COVID-19. To date, the recurrence of COVID-19 symptoms following the use of ritonavir-boosted nirmatrelvir has not been associated with progression to severe COVID-19. Therefore, concerns about the recurrence of symptoms should not be a reason to avoid using ritonavir-boosted nirmatrelvir.
• Longer treatment courses of ritonavir-boosted nirmatrelvir are not authorized by the current EUA, and there are insufficient data on the efficacy of administering a second course.

SARS-CoV-2 Resistance

• Viral mutations that lead to substantial resistance to nirmatrelvir have been selected for in vitro studies; the fitness of these mutations is unclear. Surveillance for the emergence of significant resistance to nirmatrelvir is critical.
• Severely immunocompromised patients can experience prolonged periods of SARS-CoV-2 replication, which may lead to rapid viral evolution. There are theoretical concerns that using a single antiviral agent in these patients may produce antiviral-resistant viruses. Additional studies are needed to assess this risk. The role of combination antiviral therapy or a longer treatment duration in treating patients who are severely immunocompromised is not yet known.

Monitoring and Adverse Effects

The most common adverse effects of ritonavir-boosted nirmatrelvir are dysgeusia, diarrhea, hypertension, and myalgia.

Renal impairment reduces the clearance of nirmatrelvir. In patients with suspected renal impairment, clinicians may consider checking the patient’s renal function to inform the dosing of ritonavir-boosted
nirmatrelvir. The dose should be reduced to nirmatrelvir 150 mg plus ritonavir 100 mg twice daily in patients with moderate renal impairment (i.e., those with an estimated glomerular filtration rate [eGFR] of ≥30 to <60 mL/min). Ritonavir-boosted nirmatrelvir is not recommended in patients with an eGFR of <30 mL/min until more data are available. The appropriate dose for patients with severe renal impairment has not been determined.

Ritonavir-boosted nirmatrelvir is not recommended for patients with known or suspected severe hepatic impairment (i.e., Child-Pugh Class C), and it should be used with caution in patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis. No pharmacokinetic or safety data are available for this patient population.

Considerations in Pregnancy

Pregnancy is a risk factor for severe COVID-19. However, like many clinical trials of treatments for COVID-19, the EPIC-HR trial excluded pregnant and lactating individuals. Ritonavir has been used extensively during pregnancy in people with HIV and has a favorable safety profile during pregnancy. The mechanisms of action for both nirmatrelvir and ritonavir and the results of animal studies of ritonavir-boosted nirmatrelvir suggest that this regimen can be used safely in pregnant individuals.

Ritonavir-boosted nirmatrelvir should be offered to pregnant and recently pregnant patients with COVID-19 who qualify for this therapy based on the results of a risk-benefit assessment. The risk-benefit assessment for using ritonavir-boosted nirmatrelvir in pregnant patients may include factors such as medical comorbidities, body mass index, vaccination status, and the number and severity of the risk factors for severe disease. Obstetricians should be aware of potential drug-drug interactions when prescribing this agent.

Lactation is not a contraindication for the use of ritonavir-boosted nirmatrelvir. There are no data on the use of nirmatrelvir in lactating people, but the data from animal studies are reassuring. In a prebirth-to-lactation study, an 8% decrease in body weight was observed on Postnatal Day 17 in the offspring of rats who received nirmatrelvir and had systemic exposures that were 8 times higher than the clinical exposures at the authorized human dose. This reduction in body weight was not seen in the offspring of rats that had exposures that were 5 times higher than the clinical exposures at the authorized human dose.

Studies of infants who were exposed to ritonavir through breast milk suggest that the amount of ritonavir that transfers through breast milk is negligible and not considered clinically significant. The decision to feed breast milk while taking ritonavir-boosted nirmatrelvir should take into consideration the benefits of breastfeeding, the need for the medication, any underlying risks of infant exposure to the drug, and the potential adverse outcomes of COVID-19.

Considerations in Children

For information on using ritonavir-boosted nirmatrelvir in pediatric patients, see Special Considerations in Children, Therapeutic Management of Nonhospitalized Children With COVID-19, and Therapeutic Management of Hospitalized Children With COVID-19.

Drug-Drug Interactions

Ritonavir-boosted nirmatrelvir has significant drug-drug interactions, primarily due to the ritonavir component of the combination. Boosting with ritonavir, which is a strong CYP3A inhibitor and a P-glycoprotein inhibitor, is required to increase the exposure of nirmatrelvir to a concentration that is effective against SARS-CoV-2. However, it may also increase concentrations of certain concomitant medications, thereby increasing the potential for serious and sometimes life-threatening drug toxicities. Additionally, ritonavir is an inhibitor, inducer, and substrate of various other drug-metabolizing enzymes.
and/or drug transporters.

Because ritonavir-boosted nirmatrelvir is the only highly effective oral antiviral for the treatment of COVID-19, **drug-drug interactions that can be safely managed should not preclude the use of this medication.**

The treatment course of ritonavir-boosted nirmatrelvir for COVID-19 is 5 days. CYP3A4 inhibition occurs rapidly after initiating ritonavir, with maximum inhibition occurring within 48 hours. After ritonavir is discontinued, 70% to 90% of CYP3A4 inhibition resolves within 2 to 3 days. The time to resolution of inhibition varies based on factors such as the patient’s age; therefore, resolution may take longer in some individuals, such as in adults of advanced age. When ritonavir is used for 5 days, its induction properties are less likely to be clinically relevant than when the drug is used chronically (e.g., in people who take HIV protease inhibitors).

Both nirmatrelvir and ritonavir are substrates of CYP3A. Thus, ritonavir-boosted nirmatrelvir should not be given within 2 weeks of administering a strong CYP3A4 inducer (e.g., St. John’s wort, rifampin). Ritonavir-boosted nirmatrelvir is **contraindicated** in this setting, as the delayed offset of enzyme induction can reduce the concentrations of nirmatrelvir and ritonavir, which may render the treatment ineffective against SARS-CoV-2. An alternative treatment for COVID-19 should be prescribed instead.

See [Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications](https://www.ncbi.nlm.nih.gov/pubmed/34726479) for guidance on managing potential drug-drug interactions.

**References**


