

Ritonavir-Boosted Nirmatrelvir (Paxlovid)

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Nirmatrelvir is an oral protease inhibitor that is active against M^{PRO}, a viral protease that plays an essential role in viral replication by cleaving the 2 viral polyproteins.¹ It has demonstrated antiviral activity against all coronaviruses that are known to infect humans.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.

Ritonavir-boosted nirmatrelvir is approved by the Food and Drug Administration (FDA) for the treatment of mild to moderate COVID-19 in adults who are at high risk of progressing to severe COVID-19.³ The Emergency Use Authorization (EUA) for ritonavir-boosted nirmatrelvir will continue to authorize the use of the EUA-labeled product for the treatment of nonhospitalized adolescents aged 12 to 17 years and weighing ≥ 40 kg who are at high risk of progressing to severe COVID-19.

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 with mild to moderate COVID-19 who are at high risk of disease progression (**AIIa**). Treatment should be initiated as soon as possible and within 5 days of symptom onset. For information on medical conditions that confer high risk, see the Centers for Disease Control and Prevention webpage [Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19](#).
- Ritonavir-boosted nirmatrelvir is available through an FDA EUA for the treatment of mild to moderate COVID-19 in nonhospitalized adolescents aged 12 to 17 years and weighing ≥ 40 kg.⁴ For recommendations on using ritonavir-boosted nirmatrelvir in nonhospitalized children with COVID-19, see [Therapeutic Management of Nonhospitalized Children With COVID-19](#).
- See the section titled Considerations in Patients With Severe Renal Insufficiency below for information on managing patients with COVID-19 and severe renal insufficiency.
- For a discussion of the treatment of prolonged, symptomatic COVID-19 in patients with evidence of ongoing SARS-CoV-2 replication, see the section titled Patients Who Are Immunocompromised and Have Prolonged COVID-19 Symptoms and Evidence of Ongoing Viral Replication below.

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.⁵ 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)⁶ and greater than the efficacy reported for molnupiravir (31% relative reduction).⁷ 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 people who are at low risk of progression to severe disease or in vaccinated people who are at high risk of 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 in this trial.⁸ Some observational studies have shown a benefit of using ritonavir-boosted nirmatrelvir in vaccinated individuals who were at high risk of progressing to severe COVID-19.⁹⁻¹² However, observational studies have inherent limitations. In particular, the results of these studies may be affected by residual confounding. For information on treatment considerations for vaccinated individuals, see [Therapeutic Management of Nonhospitalized Adults With COVID-19](#).

There are no data from randomized clinical trials that support the use of ritonavir-boosted nirmatrelvir in hospitalized patients with COVID-19.

For more information on the use of ritonavir-boosted nirmatrelvir in patients with COVID-19, see [Table 4e](#). 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](#) for details.

Drug-Drug Interactions

The FDA prescribing information for ritonavir-boosted nirmatrelvir includes a boxed warning about significant drug-drug interactions between ritonavir-boosted nirmatrelvir and other medications. These interactions are primarily caused by the ritonavir component of the combination. Ritonavir, a strong CYP3A4 inhibitor and a P-glycoprotein inhibitor, may increase the blood concentration of certain concomitant medications and increase the potential for serious drug toxicities. 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. Clinicians should consider both the potential benefits of treatment with ritonavir-boosted nirmatrelvir and the potential risks related to drug-drug interactions. Many drug-drug interactions between ritonavir-boosted nirmatrelvir and concomitant medications (e.g., certain statins, calcium channel blockers, or direct oral anticoagulants) **can be safely managed**. 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](#). Clinicians should be aware that the drug-drug interaction potential of ritonavir-boosted nirmatrelvir may change if it is used for extended durations (i.e., ≥ 10 days).

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](#). Box 1 lists select outpatient medications that are not expected to have clinically relevant interactions with ritonavir-boosted nirmatrelvir. 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](#)
- Tables with guidance on managing specific drug-drug interactions:
 - The [University of Waterloo/University of Toronto drug interaction guide](#) for ritonavir-boosted nirmatrelvir
 - The FDA [prescribing information](#) for ritonavir-boosted nirmatrelvir

Patients Who Are Immunocompromised and Have Prolonged COVID-19 Symptoms and Evidence of Ongoing Viral Replication

For patients who are immunocompromised and have prolonged COVID-19 symptoms and evidence of ongoing viral replication (e.g., those with a low cycle threshold value, as measured by a reverse transcription polymerase chain reaction result or with a positive rapid antigen test result) despite receiving a course of antiviral therapy, the optimal management is unknown. Case reports and case series have described the treatment of these patients with additional antiviral treatments, prolonged courses of antiviral treatments, high-titer COVID-19 convalescent plasma, or combination therapy.¹³

¹⁹ For information on potential treatment options, see [Special Considerations in People Who Are Immunocompromised](#) and [Therapeutic Management of Nonhospitalized Adults With COVID-19](#).

Viral Rebound and Symptom Recurrence

Observational studies and the EPIC-HR and MOVE-OUT trials 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 or molnupiravir.^{3,20-23} However, viral rebound can also occur in patients who have not received treatment for COVID-19.²⁴ Some observational studies have reported that patients who were treated with ritonavir-boosted nirmatrelvir had a higher frequency of viral rebound and symptom recurrence than those who did not receive treatment.^{25,26} The re-emergence of culturable SARS-CoV-2 has been reported in some individuals with viral rebound.

To date, virus detection and the recurrence of COVID-19 symptoms following the use of antiviral therapies have not been associated with progression to severe COVID-19.^{27,28} Therefore, concerns about viral rebound or the recurrence of symptoms should not be a reason to avoid using antiviral therapies when their use is indicated.^{23,29-31} There are insufficient data on whether a longer course of ritonavir-boosted nirmatrelvir will prevent viral rebound or symptom recurrence. There are also insufficient data on the efficacy of administering a second course of antiviral therapy to treat viral rebound or symptom recurrence. However, a clinical trial that is evaluating the use of a second course of ritonavir-boosted nirmatrelvir to treat patients with viral rebound and symptom recurrence is underway (ClinicalTrials.gov Identifier [NCT05567952](#)).

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, particularly in patients who are severely immunocompromised and who experience prolonged replication of SARS-CoV-2.

Additional Considerations

- Nirmatrelvir must be administered with ritonavir to achieve sufficient therapeutic plasma concentrations.
- In patients with moderate renal impairment (i.e., those with an estimated glomerular filtration rate [eGFR] of ≥ 30 to < 60 mL/min), the dose should be reduced to nirmatrelvir 150 mg with ritonavir 100 mg PO twice daily.
- 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.
- 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 may lead to the emergence of drug 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 very limited data on combining ritonavir-boosted nirmatrelvir with other antiviral therapies to treat nonhospitalized patients with COVID-19. Clinical trials are needed to determine whether combination therapy has a role in the treatment of COVID-19.
- The FDA [prescribing information](#) for ritonavir-boosted nirmatrelvir advises against crushing nirmatrelvir and ritonavir tablets. However, some data indicate that the tablets can be split or crushed if necessary.³²

Monitoring and Adverse Effects

The most common adverse effects of ritonavir-boosted nirmatrelvir are dysgeusia, diarrhea, hypertension, and myalgia. Anaphylaxis, serious skin reactions, and other hypersensitivity reactions have also been reported.

There is no need to check a patient's renal function prior to prescribing ritonavir-boosted nirmatrelvir unless the patient is suspected to have moderate to severe renal impairment (i.e., those with an eGFR of <60 mL/min). For these patients, clinicians may consider checking the patient's renal function to inform the dosing of ritonavir-boosted nirmatrelvir.

Considerations in Patients With Severe Renal Insufficiency

The FDA prescribing information states that ritonavir-boosted nirmatrelvir is not recommended for patients with an eGFR of <30 mL/min until more data are available to establish appropriate dosing.³ Additional information is available in the initial FDA Center for Drug Evaluation and Research review for the EUA of ritonavir-boosted nirmatrelvir.³³ There is limited clinical experience with the use of ritonavir-boosted nirmatrelvir in patients with an eGFR of <30 mL/min and in those who require hemodialysis.^{34,35} Based on limited data, some groups have proposed dosing adjustments for ritonavir-boosted nirmatrelvir in these patients.³⁶⁻³⁸

Considerations in Pregnant and Lactating People

See [Pregnancy, Lactation, and COVID-19 Therapeutics](#) for the Panel's guidance on the use of ritonavir-boosted nirmatrelvir during pregnancy and lactation.

Considerations in Children

Ritonavir-boosted nirmatrelvir is available through an FDA EUA for the treatment of mild to moderate COVID-19 in nonhospitalized adolescents aged 12 to 17 years and weighing ≥40 kg. For recommendations on using ritonavir-boosted nirmatrelvir in nonhospitalized children with COVID-19, see [Therapeutic Management of Nonhospitalized Children With COVID-19](#).

Clinical Data

The EPIC-HR study was a multinational randomized trial that compared the use of 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.⁵ Eligible patients were randomized within 5 days of symptom onset, were not vaccinated 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 occurred 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. 0.3% and 3% vs. 2%, respectively). Fewer ritonavir-boosted nirmatrelvir recipients discontinued the study drug due to an adverse event than placebo recipients (2% vs. 4%).

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