

Ritonavir-Boosted Nirmatrelvir (Paxlovid)

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Nirmatrelvir is an orally bioavailable 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. 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-19.³

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 and pediatric patients aged ≥ 12 years and weighing ≥ 40 kg with mild to moderate COVID-19 who are at high risk of disease progression;⁴ treatment should be initiated as soon as possible and within 5 days of symptom onset (**AIIa**).

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](#). Box 1 lists commonly prescribed outpatient medications that are not expected to have clinically relevant interactions with ritonavir-boosted nirmatrelvir, and Box 2 lists 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 [Ontario COVID-19 Science Advisory Table](#)
 - The FDA EUA [fact sheet](#) and [checklist](#) 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](#).

Rationale

The EPIC-HR trial demonstrated that starting ritonavir-boosted nirmatrelvir treatment in nonhospitalized adults with mild to moderate COVID-19 within 5 days of symptom onset reduced the risk of hospitalization or death through Day 28 by 89% compared to placebo.^{3,5} This efficacy is comparable to remdesivir (87% relative reduction)⁶ and greater than the efficacy reported for molnupiravir (30% relative reduction).⁷

Ritonavir-boosted nirmatrelvir is expected to be active against the Omicron (B.1.1.529) variant and its BA.2 subvariant,⁸ although there is currently a lack of data on the clinical efficacy of ritonavir-boosted nirmatrelvir against this variant and subvariant.⁹⁻¹¹ 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](#)).

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.⁵ 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. 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%).

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. It is unknown whether a shorter course is less effective or associated with the emergence of nirmatrelvir-resistant mutations.
- If a patient requires hospitalization after starting treatment, the full treatment course of ritonavir-boosted nirmatrelvir can be completed at the clinician's discretion.
- 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.
- 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.

- 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 severely immunocompromised patients is not yet known.
- Case reports 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. Case reports and results from the EPIC-HR trial also describe instances of increases in SARS-CoV-2 RNA levels following completion of the treatment course.^{12,13} The frequency, mechanism, and clinical implications of these events are not yet known. There are currently no data on the efficacy of administering longer courses or a second course of ritonavir-boosted nirmatrelvir.

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 with 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-19.⁴ 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 documented 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, and vaccination status. Obstetricians should be aware of potential drug-drug interactions when prescribing this agent.

Considerations in Children

Ritonavir-boosted nirmatrelvir is authorized for use in pediatric patients aged ≥ 12 years and weighing ≥ 40 kg. The EPIC-HR trial excluded persons aged < 18 years. The safety and efficacy of using ritonavir-boosted nirmatrelvir in pediatric patients has not been established in clinical trials.

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.¹⁴ After ritonavir is discontinued, 70% to 90% of CYP3A4 inhibition resolves within 2 to 3 days.¹⁵ 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 the elderly. 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).¹⁶ 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](#) for guidance on managing potential drug-drug interactions.

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