

# The COVID-19 Treatment Guidelines Panel’s Statement on Therapies for High-Risk, Nonhospitalized Patients With Mild to Moderate COVID-19

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Prior to mid-December 2021, the anti-SARS-CoV-2 monoclonal antibodies (mAbs) bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab were the only therapies recommended by the COVID-19 Treatment Guidelines Panel (the Panel) for nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease. Since then, the B.1.1.529 (Omicron) variant of concern (VOC) has become the dominant variant in many parts of the United States.<sup>1</sup> This variant, which has numerous mutations in the spike protein, is predicted to have markedly reduced susceptibility to bamlanivimab plus etesevimab and casirivimab plus imdevimab. Because sotrovimab is the only available anti-SARS-CoV-2 mAb that is anticipated to have activity against the Omicron VOC, the Panel recently added a 3-day course of intravenous (IV) remdesivir as another treatment option for this group of patients (see the Panel’s statement in [an archived version of the Guidelines](#)).

On December 22 and 23, 2021, the Food and Drug Administration (FDA) issued Emergency Use Authorizations (EUAs) that allow 2 new oral antiviral agents to be used in this patient population: ritonavir-boosted nirmatrelvir (Paxlovid) and molnupiravir.

## Ritonavir-Boosted Nirmatrelvir (Paxlovid)

Nirmatrelvir (PF-07321332) is an orally bioavailable protease inhibitor that is active against M<sup>PRO</sup>, a viral protease that plays an essential role in viral replication by cleaving the 2 viral polyproteins.<sup>2</sup> It has demonstrated antiviral activity against all coronaviruses that are known to infect humans.<sup>3</sup> Nirmatrelvir is packaged with ritonavir (as Paxlovid), a strong cytochrome P450 (CYP) 3A4 inhibitor and pharmacokinetic boosting agent. Ritonavir is required to increase nirmatrelvir concentrations to the target therapeutic ranges.

## Molnupiravir

Molnupiravir is the oral prodrug of beta-D-N4-hydroxycytidine (NHC), a ribonucleoside that has broad antiviral activity against RNA viruses. NHC uptake by viral RNA-dependent RNA-polymerases results in viral mutations and lethal mutagenesis.<sup>4,5</sup>

Molnupiravir has potent antiviral activity against SARS-CoV-2.<sup>4</sup> As a mutagenic ribonucleoside antiviral agent, there is a theoretical risk that molnupiravir will be metabolized by the human host cell and incorporated into the host DNA, leading to mutations. Molnupiravir has been evaluated in 2 in vivo rodent mutagenicity assays. One study produced results that were equivocal; in the other study, there was no evidence for mutagenicity. The FDA concluded that, based on the available genotoxicity data and the 5-day duration of treatment, molnupiravir has a low risk for genotoxicity.<sup>6</sup> In addition, there have been concerns about the potential effects of molnupiravir on SARS-CoV-2 mutation rates; the FDA is requiring the manufacturer to establish a process to monitor genomic databases for the emergence of SARS-CoV-2 variants.

## Purpose of This Statement

The purpose of this statement is to provide clinicians with guidance on the use of ritonavir-boosted nirmatrelvir (Paxlovid), sotrovimab, remdesivir, and molnupiravir for the treatment of nonhospitalized patients with COVID-19 who are at high risk of progressing to severe disease. These recommendations

are based on the results of clinical trials for ritonavir-boosted nirmatrelvir (Paxlovid), remdesivir, and molnupiravir, and on the results of clinical trials and laboratory assessments of the activity of the anti-SARS-CoV-2 mAb products that are currently available through EUAs for COVID-19 treatment.

It should be noted that a number of factors affect the selection of the best treatment option for a specific patient. These factors include, but are not limited to, the clinical efficacy of the treatment option, the availability of the treatment option, the feasibility of administering parenteral medications (i.e., sotrovimab, remdesivir), the potential for significant drug-drug interactions (i.e., the interactions associated with using ritonavir-boosted nirmatrelvir [Paxlovid]), and the regional prevalence of the Omicron VOC.

All these anti-SARS-CoV-2 therapeutics, which were evaluated initially in unvaccinated individuals, provide the greatest benefit for nonhospitalized patients who have risk factors for progression to severe COVID-19. The risks for progression are substantially higher for those who are not vaccinated or those who are vaccinated but who are not expected to mount an adequate immune response to the vaccine. When there are logistical or supply constraints that make it impossible to offer the available therapy to all eligible patients, patient triage will be necessary. Please see [the Panel's statement on prioritizing the use of outpatient therapies when there are logistical or supply constraints](#).

## Recommendations

For nonhospitalized patients with mild to moderate COVID-19 who are at high risk of disease progression,<sup>7</sup> the Panel recommends using 1 of the following therapeutics (listed in order of preference):

- **Nirmatrelvir 300 mg with ritonavir 100 mg (Paxlovid)** orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged  $\geq 12$  years and weighing  $\geq 40$  kg (**AIIa**).
  - Ritonavir-boosted nirmatrelvir (Paxlovid) has significant and complex drug-drug interactions, primarily due to the ritonavir component of the combination.
  - Before prescribing ritonavir-boosted nirmatrelvir (Paxlovid), clinicians **should carefully review the patient's concomitant medications**, including over-the-counter medications and herbal supplements, to evaluate potential drug-drug interactions. See the [Panel's statement on the drug-drug interactions for ritonavir-boosted nirmatrelvir \(Paxlovid\)](#) for details.
- **Sotrovimab 500 mg** as a single IV infusion, administered as soon as possible and within 10 days of symptom onset in those aged  $\geq 12$  years and weighing  $\geq 40$  kg who live in areas with a high prevalence of the Omicron VOC (**AIIa**).
  - If the Delta VOC still represents a significant proportion of infections in the region and other options are not available or are contraindicated, patients can be offered bamlanivimab plus etesevimab or casirivimab plus imdevimab, with the understanding that this treatment would be ineffective if they are infected with the Omicron VOC.
  - Sotrovimab should be administered in a setting where severe hypersensitivity reactions, such as anaphylaxis, can be managed. Patients should be monitored during the infusion and observed for at least 1 hour after infusion.
- **Remdesivir 200 mg IV** on Day 1, followed by **remdesivir 100 mg IV** daily on Days 2 and 3, initiated as soon as possible and within 7 days of symptom onset in those aged  $\geq 12$  years and weighing  $\geq 40$  kg (**BIIa**).
  - Because remdesivir requires IV infusion for 3 consecutive days, there may be logistical constraints to administering remdesivir in many settings.

- Remdesivir is currently approved by the FDA for use in hospitalized individuals, and outpatient treatment would be an off-label indication.
- Remdesivir should be administered in a setting where severe hypersensitivity reactions, such as anaphylaxis, can be managed. Patients should be monitored during the infusion and observed for at least 1 hour after infusion.
- **Molnupiravir 800 mg** orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged  $\geq 18$  years **ONLY** when none of the above options can be used (**CIIa**).
  - The FDA EUA states that molnupiravir is not recommended for use in pregnant patients due to concerns about the instances of fetal toxicity observed during animal studies. However, when other therapies are not available, pregnant people with COVID-19 who are at high risk of progressing to severe disease may reasonably choose molnupiravir therapy after being fully informed of the risks, particularly those who are beyond the time of embryogenesis (i.e.,  $>10$  weeks' gestation). The prescribing clinician should document that a discussion of the risks and benefits occurred and that the patient chose this therapy.
  - There are no data on the use of molnupiravir in patients who have received COVID-19 vaccines, and the risk-to-benefit ratio is likely to be less favorable because of the lower efficacy of this drug.

## Rationale

Multiple therapeutic agents are now available for nonhospitalized patients with mild to moderate COVID-19 who are at high risk of disease progression. The Panel favors the use of ritonavir-boosted nirmatrelvir (Paxlovid) in most high-risk, nonhospitalized patients with mild to moderate COVID-19. If ritonavir-boosted nirmatrelvir (Paxlovid) is not available or cannot be used because of drug interactions, then the Panel recommends using sotrovimab. If sotrovimab is not available, then the Panel recommends using remdesivir. Molnupiravir should only be administered when the other 3 options are either not available or cannot be used.

There are currently no clinical trial data that compare the clinical efficacy of these 4 therapies, and there are no data on the use of combinations of antiviral agents and/or anti-SARS-CoV-2 mAbs for the treatment of COVID-19. The rationale for the Panel's recommendations is discussed below.

### *Ritonavir-Boosted Nirmatrelvir (Paxlovid)*

In the EPIC-HR trial, ritonavir-boosted nirmatrelvir (Paxlovid) reduced the risk of hospitalization or death by 88% compared to placebo in nonhospitalized adults with laboratory-confirmed SARS-CoV-2 infection.<sup>8</sup> This efficacy is comparable to the efficacies reported for sotrovimab (i.e., 85% relative reduction),<sup>9</sup> and remdesivir (i.e., 87% relative reduction)<sup>10</sup> and greater than the efficacy reported for molnupiravir (i.e., 30% relative reduction).<sup>11</sup>

Ritonavir-boosted nirmatrelvir (Paxlovid) is expected to be active against the Omicron VOC, although in vitro and in vivo data are currently limited. Because of the potential for significant drug-drug interactions with concomitant medications, this regimen may not be a safe choice for all patients (see [the Panel's statement on these drug-drug interactions for details](#)).

### *Sotrovimab*

Several anti-SARS-CoV-2 mAb products (i.e., bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab) have received EUAs from the FDA for the treatment of nonhospitalized

patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease. In the clinical trials for these agents, anti-SARS-CoV-2 mAbs reduced the risk of hospitalization or death by 70% to 85% compared to placebo.

The Omicron VOC has become the dominant variant in many parts of the United States<sup>1</sup> and is predicted to have markedly reduced susceptibility to bamlanivimab plus etesevimab and casirivimab plus imdevimab. In vitro studies indicate that sotrovimab remains active against the Omicron VOC.<sup>12</sup>

### ***Remdesivir***

Remdesivir has been studied in nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease. The PINETREE trial showed that 3 consecutive days of IV remdesivir resulted in an 87% relative reduction in the risk of hospitalization or death compared to placebo.<sup>10</sup>

Remdesivir is expected to be active against the Omicron VOC, although in vitro and in vivo data are currently limited. Because remdesivir requires IV infusion for 3 consecutive days, there may be logistical constraints to administering remdesivir in many settings, but it is an option if ritonavir-boosted nirmatrelvir (Paxlovid) and sotrovimab are not available.

Remdesivir is currently approved by the FDA for use in hospitalized individuals, and outpatient treatment would be an off-label indication.

### ***Molnupiravir***

In the MOVE-OUT trial, molnupiravir reduced the rate of hospitalization or death by 30% compared to placebo.<sup>6</sup> Even though the different treatment options have not been directly compared in clinical trials, the Panel recommends using molnupiravir only when ritonavir-boosted nirmatrelvir (Paxlovid), sotrovimab, and remdesivir are not available or cannot be given, because molnupiravir has lower efficacy than the other options.

Molnupiravir is expected to be active against the Omicron VOC, although in vitro and in vivo data are currently limited.

## **General Considerations**

- For guidance on determining which individuals may receive the greatest benefit from therapy when there are logistical or supply constraints, see [the Panel's statement on prioritizing the use of outpatient therapies](#).
- The time from symptom onset may influence which treatment options should be used, as outlined in the Recommendations section above.
- There are no data on the use of combination antiviral therapies, or on the combination of antiviral agents and anti-SARS-CoV-2 mAbs, 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 SARS-CoV-2 infection.
- If a patient requires hospitalization after starting treatment, the full treatment course of ritonavir-boosted nirmatrelvir (Paxlovid), remdesivir, or molnupiravir can be completed at the health care provider's discretion.
- These agents may be used in patients who are hospitalized for a diagnosis other than COVID-19, provided they have mild to moderate COVID-19 and are at high risk of progressing to severe disease.

## Additional Considerations When Using Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Molnupiravir

### *Ritonavir-Boosted Nirmatrelvir (Paxlovid)*

- Nirmatrelvir must be administered with ritonavir to achieve sufficient therapeutic plasma concentrations.
- Ritonavir-boosted nirmatrelvir (Paxlovid) has numerous drug-drug interactions and the potential to cause serious or life-threatening adverse effects. **Before prescribing ritonavir-boosted nirmatrelvir (Paxlovid), clinicians should review the patients' medication list to assess the risk of drug-drug interactions.** See [the Panel's statement on the drug-drug interactions for ritonavir-boosted nirmatrelvir \(Paxlovid\)](#) for details.
- Patients should complete the 5-day treatment course of ritonavir-boosted nirmatrelvir (Paxlovid). It is unknown whether a shorter course is less effective or whether a shorter course is associated with the emergence of nirmatrelvir-resistant mutations.
- The EPIC-HR trial excluded pregnant and lactating individuals. Ritonavir has been used extensively during pregnancy in people with HIV, which suggests that it has an acceptable safety profile during pregnancy. Based on the mechanisms of action for both nirmatrelvir and ritonavir and the available animal data, the Panel would not withhold ritonavir-boosted nirmatrelvir (Paxlovid) from a pregnant patient if the potential benefits outweighed the potential risks.
- Ritonavir-boosted nirmatrelvir (Paxlovid) is authorized for use in pediatric patients aged  $\geq 12$  years and weighing  $\geq 40$  kg. The safety and efficacy of using ritonavir-boosted nirmatrelvir (Paxlovid) in pediatric patients has not been established in clinical trials.
- The dose should be reduced to nirmatrelvir 150 mg and ritonavir 100 mg twice daily in patients with moderate renal impairment (i.e., those with an estimated glomerular filtration rate [eGFR] of  $\geq 30$  to  $< 60$  mL/min). Ritonavir-boosted nirmatrelvir (Paxlovid) **is not recommended** in patients with an eGFR of  $< 30$  mL/min until more data are available.
- Ritonavir-boosted nirmatrelvir (Paxlovid) **is not recommended** in patients with 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.
- The most common adverse effects of ritonavir-boosted nirmatrelvir (Paxlovid) are dysgeusia, diarrhea, hypertension, and myalgia.

### *Molnupiravir*

- Patients should complete the 5-day treatment course of molnupiravir. It is unknown whether a shorter course is less effective or whether a shorter course is associated with the emergence of molnupiravir-resistant mutations.
- Patients of childbearing potential should be counseled about abstaining from sex or using reliable contraception for the duration of therapy and for up to 4 days after receiving molnupiravir. Reproductive toxicity has been reported in animal studies of molnupiravir, and molnupiravir may be mutagenic during pregnancy.
- Men of reproductive potential who are sexually active with individuals of childbearing potential should abstain from sex or use a reliable method of contraception for the duration of treatment **and for at least 3 months after the last dose of molnupiravir.**
- The FDA EUA states that molnupiravir is not recommended for use in pregnant patients due to concerns about fetal toxicity that are based on data from animal studies. However, when preferred

therapies are not available, pregnant people who are at high risk of progressing to severe disease may reasonably choose molnupiravir therapy after being fully informed of the risks, particularly those who are beyond the time of embryogenesis (i.e., >10 weeks' gestation). The prescribing clinician should document that a discussion of the risks and benefits occurred and that the patient chose this therapy.

- Based on the lack of data on the use of molnupiravir in lactating people and the potential for adverse effects in the infant from molnupiravir exposure, the current recommendation is to avoid feeding an infant breast milk during molnupiravir treatment and for 4 days after the final dose. Pumping and discarding breast milk to maintain supply during this time is recommended.
- There are no data available on the use of molnupiravir in children aged <18 years. Molnupiravir is not authorized for use in children aged <18 years due to potential effects on bone and cartilage growth.
- Based on in vitro studies, neither molnupiravir nor its active metabolite NHC are inhibitors or inducers of major drug-metabolizing enzymes or inhibitors of major drug transporters. According to the EUA, no drug-drug interactions have been identified for molnupiravir.
- The most common adverse effects of molnupiravir are diarrhea, nausea, and dizziness.

## Clinical Trial Data

### *Ritonavir-Boosted Nirmatrelvir (Paxlovid)*

The EPIC-HR study was a multinational, randomized trial that compared the use of ritonavir-boosted nirmatrelvir (Paxlovid) given orally twice daily for 5 days to placebo in nonhospitalized adults with mild to moderate COVID-19 who were at high risk of clinical progression. Eligible participants were randomized within 5 days of symptom onset, were unvaccinated, and had at least 1 risk factor for progression to severe disease.<sup>8</sup> Patients were excluded if they used medications that are highly dependent upon CYP3A4 for clearance or are strong inducers of CYP3A4. The primary composite outcome was COVID-19-related hospitalization or death from any cause through Day 28 among the participants who were randomized within 3 days of symptom onset.

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

Participants 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 and all-cause deaths occurred by Day 28 in 5 of 697 participants (0.72%) in the ritonavir-boosted nirmatrelvir (Paxlovid) arm and in 44 of 682 participants (6.45%) in the placebo arm. Among the 2,085 participants 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 participants (0.8%) in the ritonavir-boosted nirmatrelvir (Paxlovid) arm and in 66 of 1,046 participants (6.3%) in the placebo arm (88% relative risk reduction; -5.62% estimated absolute reduction; 95% CI, -7.21% to -4.03%;  $P < 0.0001$ ). There were no deaths in the ritonavir-boosted nirmatrelvir (Paxlovid) arm and 12 deaths in the placebo arm.

Among the 2,224 participants who were included in the EPIC-HR safety analysis set (i.e., those who received at least 1 dose of either ritonavir-boosted nirmatrelvir [Paxlovid] or placebo), the adverse events that occurred more frequently in ritonavir-boosted nirmatrelvir (Paxlovid) recipients than in placebo recipients were dysgeusia (6% vs. <1%) and diarrhea (3% vs. 2%). Fewer ritonavir-boosted nirmatrelvir (Paxlovid) recipients discontinued the study drug due to an adverse event than placebo recipients (2% vs. 4%).

## ***Sotrovimab***

The data that support the EUA for sotrovimab are from the Phase 3 COMET-ICE trial, which included outpatients aged >18 years with mild to moderate COVID-19 who were at high risk of progressing to severe COVID-19 and were within 5 days of symptom onset. The primary endpoint of the study was the proportion of participants who were hospitalized for  $\geq 24$  hours or who died from any cause by Day 29. Endpoint events occurred in 3 of 291 participants (1%) in the sotrovimab arm and in 21 of 292 participants (7%) in the placebo arm ( $P = 0.002$ ), resulting in a 6% absolute reduction and an 85% relative reduction (95% CI, 44% to 96%) in the risk of hospitalization or death among those who received sotrovimab.<sup>9,13</sup>

## ***Remdesivir***

The PINETREE study was a randomized, placebo-controlled trial in nonhospitalized patients with COVID-19 who were at high risk of clinical progression and were within 7 days of symptom onset. Nonhospitalized participants were randomized to receive 3 days of IV remdesivir or placebo. The trial was stopped early for administrative reasons.

At treatment initiation, the median duration of symptoms was 5 days. By Day 28, the primary endpoint had occurred in 2 of 279 remdesivir recipients (0.7%) and in 15 of 283 placebo recipients (5.3%), resulting in a 4.6% absolute reduction and an 87% relative reduction in the risk of hospitalization or death among those who received remdesivir (HR 0.13; 95% CI, 0.03–0.59;  $P = 0.008$ ).<sup>10</sup>

## ***Molnupiravir***

MOVE-OUT was a multinational, Phase 3, randomized trial that compared the use of molnupiravir 800 mg administered orally every 12 hours for 5 days to placebo. The participants were nonhospitalized, unvaccinated, nonpregnant adults with mild to moderate COVID-19 who were at high risk of clinical progression to severe COVID-19 and who were within 5 days of symptom onset.<sup>11</sup> The primary composite outcome was all-cause hospitalizations (defined as hospital stays that lasted >24 hours) and deaths by Day 29.

In an interim analysis that included 50% of the target accrual population, hospitalization or death occurred in 28 of 385 participants (7.3%) in the molnupiravir arm and in 53 of 377 participants (14.1%) in the placebo arm by Day 29 (adjusted difference of -6.8%; 95% CI, -11.3% to -2.4%;  $P = 0.001$ ).<sup>11</sup>

The final analysis included 1,433 participants; the median age was 43 years (with 17% aged >60 years). Forty-nine percent of the participants were men, 57% were White, 50% were Hispanic/Latino, and 5% were Black or African American. Among the participants, 74% had a body mass index  $\geq 30$  and 16% had diabetes. The time from COVID-19 symptom onset to randomization was  $\leq 3$  days in 48% of participants.

By Day 29, hospitalizations or deaths had occurred in 48 of 709 participants (6.8%) in the molnupiravir arm and in 68 of 699 participants (9.7%) in the placebo arm (30% relative risk reduction; -3.0% adjusted difference; 95% CI, -5.9% to -0.1%;  $P = 0.0218$ ).<sup>6</sup> There was 1 death in the molnupiravir arm, and there were 9 deaths in the placebo arm. There were no significant differences between the arms in the proportion of participants who experienced adverse events or serious adverse events.

The difference in the efficacy of molnupiravir that was observed between participants in the interim analysis and those enrolled after the interim analysis has not been fully explained.

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