Nirmatrelvir/ritonavir (brand name Paxlovid) has been FDA-authorized for emergency use to treat mild-to-moderate COVID-19 since December 2021.

**CLINICAL INFORMATION**

**Eligibility:** The nirmatrelvir/ritonavir EUA covers adults and pediatric patients 12 years and older weighing at least 40 kg (88 lb) who have a clinical diagnosis of COVID-19 and are at high risk for progression to severe COVID-19. Nirmatrelvir/ritonavir is not recommended for patients with severe renal impairment or Child-Pugh Class C liver impairment.

**Dosing:** Paxlovid is dispensed in blister packs that contain two 150 mg tablets of nirmatrelvir and one 100 mg tablet of ritonavir. Paxlovid dosing varies by kidney function, as below, so in some cases, only one of the nirmatrelvir tablets will be needed (a 100 mg ritonavir tablet, however, is always given alongside each nirmatrelvir dose, regardless of renal function):

<table>
<thead>
<tr>
<th>EGFR (CKD-EPI formula)</th>
<th>Dose of nirmatrelvir/ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60 mL/min</td>
<td>300 mg nirmatrelvir + 100 mg ritonavir, twice daily for 5 days*</td>
</tr>
<tr>
<td>30≤60 mL/min</td>
<td>150 mg nirmatrelvir + 100 mg ritonavir, twice daily for 5 days*</td>
</tr>
<tr>
<td>&lt;30 mL/min</td>
<td>Not recommended: Appropriate dosing has not been determined.</td>
</tr>
</tbody>
</table>

* Courses of nirmatrelvir/ritonavir longer than 5 consecutive days are not FDA-authorized.

**Clinical Decision-Making:** In ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease, FDA authorization states nirmatrelvir/ritonavir should be administered as soon as possible after diagnosis and within 5 days of symptom onset. **IDSA guidelines** suggest Paxlovid be initiated within 5 days of symptom onset (conditional recommendation, low certainty of evidence). **NIH guidelines** also suggest Paxlovid for nonhospitalized patients with mild-to-moderate COVID-19 who are at high risk of disease progression. (If a patient’s medications require dosing adjustment for safe coadministration with nirmatrelvir/ritonavir, then a pharmacist may not prescribe it. Use of nirmatrelvir/ritonavir is recommended regardless of vaccination status (Ganatra, August 2022).)

The Real-Time Learning Network’s [COVID-19 Outpatient Treatment Guidelines Roadmap](https://www.realtimelearning.net/roadmap) and HHS’s [COVID-19 Therapeutics Clinical Decision Aid](https://www.realtimelearning.net/rdma) offer paths to evaluate current U.S. treatment options.
Because this medication is co-formulated with ritonavir as a pharmacokinetic booster, and ritonavir can alter levels of many drugs, clinicians should be aware of and identify any potential drug interactions. At the same time, NIH guidelines advise that “drug-drug interactions that can be safely managed should not preclude the use of this medication.”

The following resources may aid clinical decision-making:

- **FDA Patient Eligibility Screening Checklist Tool for Prescribers [PDF]**
  This printable checklist includes a patient screening guide and lists drugs with established and/or potentially significant interactions. Drugs are listed as either contraindicated or as requiring additional management (i.e., avoiding and/or holding of the drug, dose adjustment or special monitoring).

- **IDSA Clinical Guide to Management of Nirmatrelvir/Ritonavir Drug Interactions**
  This clinical reference lists steps to take in order minimize risk of interactions and provides information on the management of commonly prescribed medications that are known to interact with nirmatrelvir/ritonavir.

- **NIH Guide to Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir & Concomitant Medications**
  This visual guide identifies outpatient medications that have clinically relevant drug-drug interactions and suggests several tiers of management strategies; it also lists commonly prescribed medications with no interactions that may be coadministered without dose adjustment/increased monitoring.

- **HIVMA Treatment Considerations for People With HIV & Hepatitis C**
  This resource outlines considerations for treating COVID-19 in people with HCV or HIV and how to handle their ART and HCV medications.

### SAFETY

The FDA EUA fact sheet for providers lists the following side effects that occurred more frequently among the clinical trial participants taking ritonavir-boosted nirmatrelvir than among those taking placebo: dysgeusia (6% and <1%, respectively), diarrhea (3% and 2%), hypertension (1% and <1%) and myalgias (1% and <1%). The proportions of subjects who discontinued treatment due to an adverse event were 2% in the ritonavir-boosted nirmatrelvir group and 4% in the placebo group.

**Viral Rebound**

A small fraction of individuals with COVID-19 who receive antiviral therapy, including Paxlovid, may experience recurrent symptoms in the first few weeks after initial improvement, a phenomenon sometimes referred to as COVID-19 rebound, which is “characterized by a recurrence of COVID-19 symptoms or a new positive viral test after having tested negative,” per a May 2022 CDC Health Alert [PDF].

Importantly, this phenomenon has been described in untreated patients as well as patients treated with other antivirals such as molnupiravir and nirmatrelvir/ritonavir. In some instances, this return of symptoms may be associated with repeat detection of virus by both antigen and culture-based tests.

There is no current certainty about whether antiviral drugs increase the rate of rebound, and rebound has not been associated with severe disease. Given the benefits afforded by drugs such as nirmatrelvir/ritonavir to reduce severe disease, these continue to be strongly recommended for high-risk people with COVID-19.
According to NIH guidelines, "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." (See Charness, September 2022; Anderson, September 2022; Soares, June 2022; Boucau, June 2022; Epling, October 2022; Deo, August 2022 – preprint, not peer-reviewed; Wang, June 2022 – preprint, not peer-reviewed). As viral rebound can be associated with culturable (i.e., transmissible) virus, CDC recommends reintroducing isolation per CDC guidance starting on the day when rebound occurs.

NIH guidelines add: “Viral rebound and the recurrence of COVID-19 symptoms can also occur in the absence of treatment with ritonavir-boosted nirmatrelvir. 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.”

According to the FDA fact sheet, this phenomenon was also observed in the clinical trials of ritonavir-boosted nirmatrelvir, in which viral rebound at day 10 or day 14 after treatment initiation occurred in 2% of participants on the study drug as well as 1.5% of participants on placebo, a difference that was not statistically significant. In the initial analysis, there was no clear signal of low drug levels or resistance to ritonavir-boosted nirmatrelvir either at baseline or after treatment and no difference in possible resistance-associated mutations between the treatment group and the placebo group. Further FDA monitoring of these events is ongoing, and more data and research are needed to properly interpret them.

**SUPPLY & ACCESS**

**Distribution:** Paxlovid is currently widely available in the U.S. For current supply information intended for health providers, see HHS’s COVID-19 Therapeutics Locator; the general public may use HHS’s Test-to-Treat locator or view HHS’s COVID-19 Public Therapeutics Locator.

**CODING & BILLING**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosage</th>
<th>Package Size</th>
<th>NDC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paxlovid EUA</td>
<td>300-100 mg</td>
<td>6 tablets</td>
<td>00069-1085-06</td>
</tr>
<tr>
<td>Paxlovid EUA</td>
<td>300-100 mg</td>
<td>30 tablets</td>
<td>00069-1085-30</td>
</tr>
</tbody>
</table>

**Billing:** Paxlovid has been added by the Health and Human Services Commission to the Medicaid and Children’s Health Insurance Program formularies as a payable pharmacy benefit.

**FURTHER INFORMATION**

Real-Time Learning Network Paxlovid Literature Reviews
FDA Paxlovid EUA Fact Sheet for Healthcare Providers
NIH Paxlovid Treatment Guidelines
HHS Fact Sheet on Paxlovid Eligibility and Effectiveness [PDF]
HIVMA Considerations for People With HIV and Hepatitis C