

The COVID-19 Treatment Guidelines Panel's Statement on Omicron Subvariants, Pre-Exposure Prophylaxis, and Therapeutic Management of Nonhospitalized Patients With COVID-19

Last Updated: November 10, 2022

The Centers for Disease Control and Prevention (CDC) has reported a rapid increase in the circulation of certain SARS-CoV-2 Omicron subvariants in the United States that are likely to be resistant to currently used anti-SARS-CoV-2 monoclonal antibodies (mAbs).¹ The subvariants BQ.1 and BQ.1.1 are likely to be resistant to bebtelovimab,² and the subvariants BA.4.6, BA.2.75.2, BA.5.2.6, BF.7, BQ.1, and BQ.1.1 are likely to be resistant to tixagevimab plus cilgavimab (Evusheld). The anticipated loss of susceptibility is based on knowledge about amino acid mutations that confer resistance to anti-SARS-CoV-2 antibodies and on data from in vitro neutralization studies.³

In this statement, the COVID-19 Treatment Guidelines Panel (the Panel) provides interim recommendations for the use of tixagevimab plus cilgavimab and bebtelovimab. The Panel will closely monitor the prevalence of circulating subvariants with markedly reduced susceptibility to these anti-SARS-CoV-2 mAbs. The recommendations on the use of bebtelovimab for the treatment of COVID-19 and on the use of tixagevimab plus cilgavimab for pre-exposure prophylaxis (PrEP) will be updated if the prevalence of these subvariants changes.

Summary Recommendations

For Pre-Exposure Prophylaxis

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends that all patients who are eligible to receive tixagevimab plus cilgavimab (Evusheld) as pre-exposure prophylaxis (PrEP) should receive bivalent COVID-19 vaccines unless the use of these vaccines is contraindicated due to a history of severe adverse reactions to a COVID-19 vaccine or any of its components **(AIII)**.
- The prevalence of Omicron subvariants that are resistant to tixagevimab plus cilgavimab is rapidly increasing. The proportion of SARS-CoV-2 infections caused by these subvariants is currently estimated to exceed 45% in all regions in the United States.
- Tixagevimab plus cilgavimab is the only agent authorized by the Food and Drug Administration for use as COVID-19 PrEP in people who are not expected to mount an adequate immune response to COVID-19 vaccination or those with contraindications for COVID-19 vaccines.
 - In the absence of an alternative option for PrEP, the Panel continues to recommend the use of **tixagevimab plus cilgavimab** as PrEP for eligible individuals **(BIIB)**. See [Prevention of SARS-CoV-2 Infection](#) for more information.
 - Given the increasing prevalence of these resistant SARS-CoV-2 subvariants, the decision to administer tixagevimab plus cilgavimab to a given patient should be based on the regional prevalence of the resistant subvariants, the individual patient's risks, the available resources, and logistics.
 - Individuals who receive tixagevimab plus cilgavimab as PrEP should continue to take precautions to avoid exposure to SARS-CoV-2. If they experience signs and symptoms consistent with COVID-19, they should be tested for SARS-CoV-2 infection and, if infected, promptly seek medical attention and treatment, if appropriate.

For Treatment of Mild to Moderate COVID-19 in Nonhospitalized Adults Who Are at High Risk of Progressing to Severe COVID-19

- The Panel has recommended bebtelovimab as an alternative treatment for COVID-19 when neither of the preferred treatments (ritonavir-boosted nirmatrelvir [Paxlovid] or remdesivir) are available, feasible to use, or clinically appropriate. However, when resistant Omicron subvariants (e.g., BQ.1, BQ.1.1) represent the majority^a of infections in the region,^{b,c} clinicians cannot rely on bebtelovimab to be effective for the treatment of COVID-19. Ritonavir-boosted nirmatrelvir, remdesivir, and molnupiravir are expected to be active against these resistant subvariants.

Summary Recommendations, continued

- The Panel continues to recommend the following anti-SARS-CoV-2 therapies as preferred treatments for COVID-19. These drugs are listed in order of preference:
 - **Ritonavir-boosted nirmatrelvir (Paxlovid) (AIIa)**
 - **Remdesivir (BIIa)**
- The following alternative therapies should be used **ONLY** when neither of the preferred therapies are available, feasible to use, or clinically appropriate. These drugs are listed in alphabetical order:
 - **Bebtelovimab**, but **ONLY** when the majority^a of circulating Omicron subvariants in the region^{b,c} are susceptible (**CIII**)
 - **Molnupiravir (CIIa)**

Rating of Recommendations: A = Strong; B = Moderate; C = Weak

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

^a The Panel acknowledges that the Centers for Disease Control and Prevention's (CDC) prevalence reports for SARS-CoV-2 subvariants are only estimates and that there is currently no definitive prevalence threshold for resistant subvariants that determines when the use of bebtelovimab for the treatment of COVID-19 will be ineffective. When the majority (>50%) of isolates in a region are likely to be resistant, the ongoing use of bebtelovimab may no longer be justified.

^b See the CDC [COVID Data Tracker](#) for regular updates on the regional proportions of SARS-CoV-2 variants in the United States.

^c Clinicians should also consider a patient's recent travel (i.e., where the patient is thought to have acquired SARS-CoV-2 infection) when reviewing regional proportions of SARS-CoV-2 variants to guide treatment.

Strategies to Facilitate the Use of Preferred Anti-SARS-CoV-2 Therapies

Ritonavir-Boosted Nirmatrelvir (Paxlovid)

- Because ritonavir is a strong cytochrome P450 3A4 inhibitor and a P-glycoprotein inhibitor, it may increase blood concentrations of certain concomitant medications.
- Many drug-drug interactions between ritonavir-boosted nirmatrelvir and concomitant medications **can be safely managed** (e.g., with certain statins, calcium channel blockers, or direct oral anticoagulants). If a significant drug-drug interaction is identified, prescribers should consider consulting with a pharmacist to facilitate the use of ritonavir-boosted nirmatrelvir. The following resources are available to assist in identifying and managing drug-drug interactions:
 - [Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir \(Paxlovid\) and Concomitant Medications](#)
 - The [Liverpool COVID-19 Drug Interactions website](#)
 - The [Ontario COVID-19 Science Advisory Table](#)
 - The Food and Drug Administration (FDA) Emergency Use Authorization (EUA) [fact sheet](#) and [checklist](#) for ritonavir-boosted nirmatrelvir
- The use of ritonavir-boosted nirmatrelvir may be challenging in patients with severe renal impairment and patients who are receiving certain transplant-related immunosuppressants or chemotherapy.
 - The EUA states that ritonavir-boosted nirmatrelvir is not recommended in patients with an estimated glomerular filtration rate (eGFR) of <30 mL/min until more data are available.⁴ Based on limited data, some groups have proposed dosing adjustments that can be used in

patients with an eGFR <30 mL/min or in patients who are on hemodialysis.⁵⁻⁹

- In patients who are receiving calcineurin and mammalian target of rapamycin inhibitors, the decision to prescribe ritonavir-boosted nirmatrelvir should always be made in consultation with the patient's specialist providers. Ritonavir-boosted nirmatrelvir may be prescribed safely in select patients if an expert in managing the interaction is available and close therapeutic drug monitoring is logistically feasible. Otherwise, an alternative therapy for COVID-19 should be considered. See the [American Society of Transplantation's statement](#) for additional information.
- Interactions between ritonavir-boosted nirmatrelvir and chemotherapeutic agents should also be managed in consultation with the patient's specialist providers. For guidance on managing these interactions, please refer to the [FDA EUA fact sheet](#) and the prescribing information for the chemotherapeutic agent. The [University Health Network/Kingston Health Sciences Centre](#) provides an additional resource for evaluating drug-drug interactions between ritonavir-boosted nirmatrelvir and chemotherapeutic agents.

Remdesivir

- Clinicians may consider preferentially using the lyophilized powder formulation of remdesivir (which contains less sulfobutylether beta-cyclodextrin sodium than the solution formulation) in patients with renal impairment. The FDA product label does not recommend using remdesivir in patients with an eGFR of <30 mL/min. However, some data suggest that remdesivir can be used in patients with an eGFR of <30 mL/min if the potential benefits outweigh the risks.¹⁰⁻¹³ See [Remdesivir](#) for more information.
- Because remdesivir requires intravenous infusions for 3 consecutive days, there may be logistical constraints to administering remdesivir in many settings. Advanced planning (e.g., reserving infusion slots, identifying alternative infusion sites) may be needed to increase access to remdesivir.
- Remdesivir can be given in skilled nursing facilities, home health care settings, and outpatient facilities such as infusion centers.

References

1. Centers for Disease Control and Prevention. Variant proportions. 2022. Available at: <https://covid.cdc.gov/covid-data-tracker/#variant-proportions>. Accessed October 18, 2022.
2. Food and Drug Administration. Fact sheet for healthcare providers: Emergency Use Authorization for bebtelovimab. 2022. Available at: <https://www.fda.gov/media/156152/download>.
3. Cao Y, Jian F, Wang J, et al. Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution. *bioRxiv*. 2022;Preprint. Available at: <https://www.biorxiv.org/content/10.1101/2022.09.15.507787v4>.
4. Food and Drug Administration. Emergency Use Authorization (EUA) for Paxlovid (nirmatrelvir tablets co-packaged with ritonavir tablets): Center for Drug Evaluation and Research (CDER) review. 2021. Available at: <https://www.fda.gov/media/155194/download>.
5. Antoine Brown P, McGuinty M, Argyropoulos C, et al. Early experience with modified dose nirmatrelvir/ritonavir in dialysis patients with coronavirus disease-2019. *medRxiv*. 2022;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2022.05.18.22275234v1>.
6. Toussi SS, Neutel JM, Navarro J, et al. Pharmacokinetics of oral nirmatrelvir/ritonavir, a protease inhibitor for treatment of COVID-19, in subjects with renal impairment. *Clin Pharmacol Ther*. 2022;112(4):892-900. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35712797>.
7. University of Liverpool. Guidance for Paxlovid dosing in patients with renal disease and patients on dialysis.

2022. Available at: https://covid19-druginteractions.org/prescribing_resources. Accessed November 7, 2022.
8. Ontario Health. COVID-19 supplemental clinical guidance #4: nirmatrelvir/ritonavir (Paxlovid) use in patients with advanced chronic kidney disease and patients on dialysis with COVID-19. 2022. Available at: <https://www.ontariohealth.ca/sites/ontariohealth/files/2022-04/PaxlovidClinicalGuide.pdf>.
 9. Hiremath S, McGuinty M, Argyropoulos C, et al. Prescribing nirmatrelvir/ritonavir for COVID-19 in advanced CKD. *Clin J Am Soc Nephrol*. 2022;17(8):1247-1250. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35680135>.
 10. Remdesivir (Veklury) [package insert]. Food and Drug Administration. 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214787Orig1s015lbl.pdf.
 11. Cheng M, Fowler R, Murthy S, et al. Remdesivir in patients with severe kidney dysfunction: a secondary analysis of the CATCO randomized trial. *JAMA Netw Open*. 2022;5(8):e2229236. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36036936>.
 12. Davoudi-Monfared E, Ahmadi A, Karimpour-Razkenari E, et al. Remdesivir administration in COVID-19 patients with renal impairment: a systematic review. *Am J Ther*. 2022;29(5):e520-e533. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35984955>.
 13. Sunny S, Samaroo-Campbell J, Abdallah M, Luka A, Quale J. Is remdesivir safe in patients with renal impairment? Experience at a large tertiary urban medical center. *Infection*. 2022:1-6. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35616879>.