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CD Summary

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# COVID-19 THERAPEUTICS FOR NON-HOSPITALIZED PATIENTS: WHAT YOU NEED TO KNOW

Vaccines and non-pharmaceutical interventions have played a huge role in efforts to decrease the health burden of COVID-19 so far. What's out there as far as treatment or prevention of SARS-CoV-2 infection among those who are unlikely to respond to vaccine or have medical contraindications to it? In this issue of the *CD Summary*, we give you the low-down on medications currently available to treat or prevent COVID-19 illness.

## TREATMENT OF MILD-TO-MODERATE COVID-19 IN PATIENTS AT HIGH RISK FOR SEVERE ILLNESS

There are several options here. Most are new and currently in limited supply. Oregon Health Authority (OHA) has been tasked by the federal government with allocating these medications at the state level. OHA is committed to doing so in a way that ensures access to cultural communities that have been hit hardest by severe COVID-19 illness. As supplies increase, access to these medications will broaden.

The following medications are authorized for use in patients ill with mild-to-moderate, laboratory-confirmed COVID-19 who are at high risk for severe COVID illness due to age or underlying conditions. These medications, in preferred order of use when they are available, as recommended by the National Institutes of Health (NIH), are:

**Nirmatrelvir/Ritonavir** (aka Paxlovid™) – This is an oral antiviral medication. Nirmatrelvir is a protease inhibitor active against SARS-CoV. Ritonavir is another protease inhibitor added to decrease the rate of nirmatrelvir metabolism. Together, they are very effective at disrupting SARS-CoV-2 replication. In randomized controlled trials, Paxlovid™ reduced risk of hospitalization or death among COVID-19 patients at high risk by 88% compared to placebo. Initial studies suggest good efficacy against the Omicron variant. Treatment is authorized for use in adults and in pediatric patients ≥12 years old and weighing ≥40 kg. It should be given within five days of symptom onset to be effective. Paxlovid™ is contraindicated in those with severe hepatic or renal disease (GFR<30 mL/min), and should be used with caution in patients taking medications that are highly dependent on CYP3A for clearance, which include a variety of statins, analgesics, neuroleptics, and anticonvulsants (in short, more medications than you can shake a stick at), due to potentially dangerous drug-drug interactions. A tool useful in identifying these interactions is available at: www.covid19-druginteractions.org/.

Remdesivir – If Paxlovid™ is not available or otherwise feasible to use, NIH recommends a three-day course of intravenous remdesivir. This medication is FDA licensed and approved, and is available through pharmaceutical distributors. In high-risk folks with mild-to-moderate COVID-19, remdesivir decreased risk of hospitalization or death by 87% compared to placebo. Treatment should be initiated within 7 days of symptom onset. Treatment is approved for adults as well as children ≥12 years old and weighing ≥40 kg. It can be used under an EUA for children weighing between 3.5 kg and 40 kg.For information on pediatric dosing under the EUA, see the FDA Provider Fact Sheet at the link, below.

**Molnupiravir** – If the above medications are unavailable or contraindicated, or there are unsurmountable logistical barriers to their use, there is another antiviral option, molnupiraivir. Named after Thor's awesomely powerful hammer, Mjölnir, this is a nucleoside analog that disrupts replication of SARS-CoV-2 viral RNA, effectively preventing the virus from multiplying. Alas, unlike its namesake, molnupiravir isn't all-powerful. Still, it has shown some efficacy. In clinical trials, molnupiravir reduced risk of hospitalization or death among high-risk COVID-19 patients by 30% compared to placebo, which is certainly better than nothing. It appears to be active against Omicron. Treatment should begin within five days of symptom onset in order to be effective. This medication is mutagenic; it is authorized for use only in adults and is not recommended in pregnant women or those who are breastfeeding due to concerns about possible effects on infant bone and cartilage formation.

## BUT WAIT! THERE'S MORE!

A new monoclonal antibody, bebtelovimab (Who comes *up* with these names, *anyway??*) was recently made available under an EUA. It is given by IV push over at least 30 seconds; and, based on Phase 2 clinical trials, it appears to be relatively safe. As with the medicines above, it is authorized for use in treatment of laboratory-confirmed, mild-to-moderate COVID-19 in patients at high risk for severe COVID illness. The EUA authorizes use in adults and in children ≥12 years of age who weigh at least 40 kg. Treatment should be started within seven days of symptom onset. *In vitro* studies suggest that bebtelovimab is active against Omicron. Unfortunately, evidence is scanty that it actually decreases risk of hospitalization or death. Bebtelovimab does appear to decrease viral load by 34% and to improve symptoms, but Phase 3 efficacy data aren't yet available.

Bebtelovimab is in limited supply and will be available through OHA allocation until supplies increase.

Three monoclonal antibody medications, sotrovimab, bamlanivimab/etesevimab, and casirivimab/imdevimab, were previously available, but the EUAs for them were suspended, as they are ineffective against one or more Omicron strains. If other strains against which these medications are effective gain prominence, we might see them back in action.

## PRE-EXPOSURE PROPHYLAXIS

Though it can't replace vaccination, there is a long-acting antibody combination called tixagevimab/cilgavimab (aka Evusheld™) now available under an EUA for pre-exposure COVID-19 prophylaxis. It is given by the intramuscular route and is indicated for patients without COVID-19 or known exposure to it who are either moderately to severely immunocompromised or have a medical contraindication to COVID-19 vaccines. The component monoclonal antibodies come in separate vials and should be injected sequentially into separate sites, preferably the gluteal muscles. In clinical trials, Evusheld™ reduced the risk of symptomatic COVID-19 in the six months following injection by 77% compared with placebo. It's worth noting that there was a higher rate of cardiovascular events among those with underlying cardiac disease who received Evusheld™ compared to those with cardiac disease in the placebo group. Though there is not a clear causal relationship, it is recommended to counsel patients with underlying CVD about this possible risk.

## ACCESS TO THESE PRODUCTS

As noted, all of these products other than remdesivir are in limited supply. As production increases, OHA will work to broaden availability. Molnupiravir and Evusheld™ are relatively more plentiful, if one can call 3,000 to 4,000 courses every two weeks "plentiful." If you are interested in obtaining these medications for your practice, please check out our COVID-19 monoclonal antibody and antiviral webpages. They include a Providers Manual that will explain how to register and place orders. If you have other questions, just send us an e-mail at OHA.therapeutics@dhsoha.state.or.us

## POST-EXPOSURE PROPHYLAXIS

No options for post-exposure prophylaxis are currently available. Although casirivimab/imdevimab and bamlanivimab/etesevimab had received EUA for post-exposure prophylaxsis, they are not effective against Omicron.

**Table 1. COVID-19 Treatment Options**

| Therapeutic agent | Dose | Prevention of hospitalizations or death over 28 days | Clinical Considerations |
|---|---|---|---|
| Ritonavir-boosted Nirmatrelvir (PAXLOVID™) | Nirmatrelvir 300 mg (nirmatrelvir 150 if eGFR ≥30 to <60 mL/min) plus ritonavir 100 mg, orally twice daily for 5 days | • ARR: 6.3% > 0.8%<br>• RRR: 88% | • Significant drug-drug interactions<br>• Ritonavir safe in pregnancy<br>• Dose adjustment for renal impairment<br>• Administer ASAP within 5 days of symptom onset |
| Remdesivir (VEKLURY®)[4] | 200 mg IV day 1, 100 mg IV on Days 2 and 3; each dose given over 30—120 minutes | • ARR: 5.3% > 0.7%<br>• RRR: 87% | • IV infusion for 3 consecutive days<br>• Administer ASAP within 7 days of symptom onset<br>• Only commercially available option |
| Molnupiravir[5] | 800 mg, orally twice daily for 5 days | • ARR: 9.7% > 6.8%<br>• RRR: 30% | • Option if other therapies unavailable[1]<br>• Concern for mutagenicity (theoretical)<br>• Avoid in pregnancy, children, and when breastfeeding<br>• Start within 5 days of symptom onset |
| Bebtelovimab | 175 mg, IV over at least 30 seconds. | • Decreases viral load<br>• Efficacy data on reduction of hospitalization and mortality risk pending | • Option if other therapies unavailable[1]<br>• Appears safe in phase 1 and 2 trials<br>• *in vitro* activity against Omicron BA.2<br>• Start within 7 days of symptom onset |

Abbreviations: ARR = absolute risk reduction; ASAP = as soon as possible; eGFR = estimated glomerular filtration rate; IV = intravenous; mAbs = monoclonal antibodies; RRR = relative risk reduction

**TABLE 2. COVID-19 Pre-exposure Prophylaxis**

| Therapeutic agent | Dose | Prevention of symptomatic COVID-19 over six months | Clinical Considerations |
|---|---|---|---|
| Tixagevimab and cilgavimab (EVUSHELD)[6] | Tixagevimab 300 mg and cilgavimab 300 mg, IM sequentially in separate sites, preferably the gluteal muscles | • ARR: 6.3% -> 0.8%<br>• RRR: 88% | • No dose adjustments needed<br>• Caution with use in CVD<br>• Do not administer within 2 weeks of COVID-19 vaccine<br>• May repeat dosing every 6 months |
| Abbreviations: ARR = absolute risk reduction; ASAP = as soon as possible; eGFR = estimated glomerular filtration rate; IV = intravenous; mAbs = monoclonal antibodies; RRR = relative risk reduction | | | |

## FDA PROVIDER FACT SHEETS

- Nirmatrelvir/ritonavir: www.fda.gov/media/155050/download
- Remdesivir: www.fda.gov/media/137566/download
- Molunupiravir: www.fda.gov/media/155054/download
- Bebtelovimab: www.fda.gov/media/156152/download
- Tixagevimab/clilgavimab: www.fda.gov/media/154701/download
- Sotrovimab: www.fda.gov/media/149534/download
- Bamlanivimab/etesevimab www.fda.gov/media/145802/download
- Casirivimab/imdevimab www.fda.gov/media/145611/download

## REFERENCES


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2. U.S. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Paxlovid™ (nirmatrelvir tablets; ritonavir tablets). Available at: www.fda.gov/media/155050/download. Accessed March 1, 2022.
3. Gupta A, Gonzalez-Rojas Y, Juarez E, Casal MC, et al. Early treatment of Covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. N Engl J Med. 2021; 385: 1941–50.
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6. U.S. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Evusheld™ (tixagevimab co-packaged with cilgavimab). Available at: www.fda.gov/media/154701/download. Accessed: March 1, 2022.



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