MAGIC's Alliance for Clinical Excellence (ACE)
Guidance to LTC Clinicians on Oral Treatment for COVID-19

We are pleased to present Guidance to LTC Clinicians on Oral Treatment for COVID-19. We are excited that oral antivirals will be available to residents in SNFs; some already have these available if the facility is part of a larger hospital system that has been receiving allocation, but this will be expanding to LTC pharmacies that serve remaining SNFs in the state.

We recommend that medical directors and facilities work together to come up with a process for when providers want to consider treatment for COVID-19 with oral antivirals. Deciding if and how to use these medications is based on prescriber judgment for an individual patient. Because these medications are new and have strict criteria for use as well as **significant drug-drug interactions**, it is important to be careful yet timely in initiating the process of treatment decision-ordering-administering.

Remember these oral antivirals are for use in mild-moderate COVID-19. The goal is to reduce risk of severe disease/hospitalization. If patients are severely ill, are on hospice or hospice-appropriate, or meet criteria for severe Covid-19 – hypoxic, requiring oxygen *or* more than their usual rate of oxygen – then these oral medications are not indicated.

MAGIC's Alliance for Clinical Excellence (ACE)

https://www.minnesotageriatrics.org/

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Minnesota Association of Geriatrics Inspired Clinicians

Guidance to LTC Clinicians on Oral Treatment for COVID-19

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Up to date as of 3/23/22

This guidance addresses ORAL antiviral therapy for COVID + patients with mild-moderate illness who are at risk for progression to severe COVID-19.

Facility preparatory process:

1. Facility should confirm their pharmacy partner is registered as a COVID oral therapeutics dispenser (either through the federal Test to Treat program or through state distribution, and has drug available)
    - All pharmacies are eligible to participate but need to register
    - Utilize your affiliated pharmacist to assist with dosing decisions if possible

Process after facility confirms partner pharmacy has oral treatment available:

1. Prescriber considers patient for oral antiviral treatment and **reviews all contraindications before prescribing**
2. Prescriber documents conversation with patient or family (requirement of EUA)
3. Prescriber contacts consultant pharmacist to review concomitant medications
    a. If consultant pharmacist is not available, contact pharmacist with partnering pharmacy
4. Prescriber orders medication via usual facility ordering process (in patient chart) with ASAP note
5. Pharmacy expedites
6. Facility staff confirm medication arrives and is given at appropriate time
    a. After appropriate period of holding any meds that need to be held

Resources For Prescribing

Current oral antiviral treatment options include **Paxlovid** (Nirmatrelvir/Ritonavir) and **Molnupiravir** (Lagevrio). Neither are currently FDA approved and both would be administered under an **EUA (emergency use authorization)**. This requires informed consent.

Please see the links to the IDSA treatment guidelines road map and NIH treatment guidelines for **a broad overview** of COVID-19 outpatient treatment options.

IDSA treatment guidelines road map:

https://www.idsociety.org/globalassets/covid-19-real-time-learning-network/outpatientroadmap-v10.pdf

NIH COVID-19 treatment guidelines:

https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults--therapeutic-management/

Consideration of Oral Antiviral Treatment

- Patient should be SYMPTOMATIC with MILD-MODERATE COVID-19, with a POSITIVE SARS-CoV-2 test and at risk for severe COVID-19 (see IDSA guideline above)
- Patient should be within 5 DAYS OF SYMPTOM ONSET – give medication ASAP within 5 day window
- Per NIH, the definition of mild and moderate COVID-19 is as follows:
    - *Mild Illness:* any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.
    - *Moderate Illness:* evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO_2) ≥94% on room air at sea level

Efficacy of Oral Antiviral Treatments

Paxlovid – EPIC-HR trial: Paxlovid reduced hospitalization and death by **88%** compared to placebo
https://www.fda.gov/media/155050/download

Molnupiravir – MOVe-OUT trial: Molnupiravir reduced hospitalization or death by **30%** compared to placebo
https://www.fda.gov/media/155054/download

NIH 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.

Administration

Paxlovid (nirmatrelvir/ritonavir) Fact_Sheet_HCP.pdf (covid19oralrx-hcp.com)

- Must be at least 40kg
- Dose: 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together orally twice daily for 5 days; with or without food
- Dose adjustment if eGFR ≥30 to <60ml/min – reduce dose to 150/100mg twice daily for 5 days
- Not approved for severe renal impairment: Avoid if eGFR<30ml/min
- Not approved for severe hepatic impairment (Child-Pugh Class C)
- Use with caution if pre-existing liver disease, liver enzyme abnormalities, or hepatitis (no safety data available)
- **Drug Interactions: IMPORTANT significant risk for drug interactions; concomitant meds should be carefully reviewed for interactions, including herbal and over the counter medications**
    - Consult https://covid19-druginteractions.org/checker
    - See the following link and/or attached addendum of medications with known high risk of interactions with Paxlovid: https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/

Molnupiravir (Lagevrio) FACT SHEET FOR HEALTHCARE PROVIDERS: EUA FOR MOLNUPIRAVIR (fda.gov)

- Dose: 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days; with or without food
- Drug Interactions: https://covid19-druginteractions.org/checker

Monitoring and Adverse Effects

- **Paxlovid**: impaired sense of taste, diarrhea, high blood pressure, muscle aches
- **Molnupiravir**: diarrhea, nausea, dizziness, erythema of skin, skin rash, urticaria, hypersensitivity (anaphylaxis, angioedema). If hypersensitivity occurs, immediately discontinue & begin appropriate meds/supportive care.

ADDENDUM

IMPORTANT there is significant risk for drug interactions with Paxlovid; other patient medications MUST be carefully reviewed for potential interactions, including herbal and over the counter medications.

NIH COVID Treatment Guideline: Last updated February 24, 2022
Ritonavir-Boosted Nirmatrelvir (Paxlovid) | COVID-19 Treatment Guidelines (nih.gov)

Prescribe an Alternative COVID-19 Therapy for cases where drug-drug interaction management strategies are not possible or feasible, or the potential risks of such strategies outweigh the potential benefits.

- Amiodarone
- Apalutamide
- Bosentan
- Carbamazepine
- Clopidogrel[a]
- Clozapine
- Disopyramide
- Dofetilide
- Dronedarone
- Enzalutamide
- Eplerenone
- Ergot derivatives
- Flecainide
- Glecaprevir/pibrentasvir
- Ivabradine
- Lumacaftor/ivacaftor
- Lumateperone
- Lurasidone
- Meperidine (pethidine)
- Midazolam (oral)
- Phenobarbital
- Phenytoin
- Pimozide
- Primidone
- Propafenone
- Quinidine
- Rifampin
- Rifapentine
- Sildenafil for PH
- St. John's wort
- Tadalafil for PH
- Tolvaptan
- Vardenafil for PH
- Voclosporin

Temporarily Withhold Concomitant Medication, If Clinically Appropriate
For guidance on restarting concomitant medication, consult the Liverpool COVID-19 Drug Interactions website.[b]
If withholding is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy.

- Alfuzosin
- Aliskiren
- Atorvastatin
- Avanafil
- Chemotherapy[c]
- Clonazepam[d]
- Clorazepate[d]
- Colchicine[e]
- Diazepam[d]
- Eletriptan
- Erythromycin
- Estazolam[d]
- Everolimus[f]
- Finerenone
- Flibanserin
- Flurazepam[d]
- Lomitapide
- Lovastatin
- Naloxegol
- Ranolazine
- Rimegepant
- Rivaroxaban[g]
- Rosuvastatin
- Salmeterol
- Silodosin
- Simvastatin
- Sirolimus[f]
- Suvorexant
- Tacrolimus[f]
- Ticagrelor
- Triazolam[d]
- Ubrogepant
- Vorapaxar

Adjust Concomitant Medication Dose and Monitor for Adverse Effects
Consult the Liverpool COVID-19 Drug Interactions website[b] for guidance. **If the dose of the concomitant medication cannot be adjusted, withhold the medication (if clinically appropriate) or use an alternative concomitant medication or COVID-19 therapy.**

- Alprazolam[d]
- Amlodipine
- Apixaban
- Aripiprazole
- Brexpiprazole
- Buspirone
- Cariprazine
- Chlordiazepoxide[d]
- Cilostazol
- Clarithromycin
- Clobazam[d]
- Cyclosporine[f]
- Darifenacin
- Digoxin
- Elexacaftor/tezacaftor/ivacaftor
- Eluxadoline
- Fentanyl
- Iloperidone
- Itraconazole
- Ivacaftor
- Ketoconazole
- Maraviroc
- Mexiletine
- Oxycodone
- Pimavanserin
- Quetiapine
- Rifabutin
- Riociguat
- Saxagliptin
- Sildenafil for ED
- Ruxolitinib
- Tadalafil for ED
- Tamsulosin
- Tezacaftor/ivacaftor
- Trazodone
- Vardenafil for ED

[a] Reduced effectiveness of clopidogrel is likely. Do not coadminister clopidogrel in patients who are at a very high risk of thrombosis (e.g., those who are within 6 weeks of coronary stenting); consider prescribing an alternative antiplatelet (i.e., prasugrel) or an alternative COVID-19 therapy. For other indications, it may be acceptable to continue clopidogrel if the benefit of ritonavir-boosted nirmatrelvir treatment outweighs the risk of reduced clopidogrel effectiveness.

[b] Additional resources include the EUA fact sheet for ritonavir-boosted nirmatrelvir and the FDA prescribing information for the concomitant medication. These may be consulted for medications that are not found on the Liverpool COVID-19 Drug Interactions website.

[c] Ritonavir-boosted nirmatrelvir may increase concentrations of certain anticancer agents, leading to an increased potential for drug toxicities. These anticancer agents include kinase inhibitors (e.g., abemaciclib, ceritinib, dasatinib, ibrutinib, neratinib, nilotinib), the IDH1 inhibitor ivosidenib, the BCL-2 inhibitor venetoclax, and vinca alkaloids (e.g., vinblastine, vincristine). Please refer to the prescribing information for the anticancer agent and consult the patient's specialist provider. Avoid concomitant administration of ritonavir-boosted nirmatrelvir with ibrutinib, neratinib, ivosidenib, or venetoclax.

[d] Abrupt discontinuation or rapid dose reduction of benzodiazepines may precipitate acute withdrawal reactions.[14] The risk is greatest for patients who have been using higher doses of benzodiazepines over an extended period of time.

[e] Colchicine is contraindicated in patients with severe hepatic or renal impairment due to the potential for serious or life-threatening reactions.

[f] Before prescribing ritonavir-boosted nirmatrelvir to a patient who is receiving this immunosuppressant, consult the patient's specialist provider(s). This immunosuppressant has significant drug-drug interaction potential with ritonavir, and close monitoring may not be feasible. See this statement from the American Society of Transplantation for more information.

[g] If the patient has a high risk of arterial or venous thrombosis (e.g., those who are within 3 months of a stroke, those with a CHA_2DS_2-VASc score of 7–9, those who are within 1 month of a pulmonary embolism), the patient's primary or specialty provider should be consulted; consider using an alternative anticoagulant or COVID-19 therapy.

Key: BCL-2 = B cell lymphoma 2; CYP = cytochrome P450; ED = erectile dysfunction; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IDH1 = isocitrate dehydrogenase-1; PH = pulmonary hypertension