FOCUS ON
PHARMACISTS PRESCRIBING COVID-19 THERAPEUTICS

This resource is designed to offer pharmacists a concise and accurate tool for assessing patient eligibility for pharmacist-prescribed nirmatrelvir/ritonavir, including identifying and managing drug interactions.

Introduction

On January 27, 2020, the Secretary of Health and Human Services (HHS), Alex M. Azar II, declared a public health emergency because of the spread of coronavirus disease 2019 (COVID-19). Since then, the order has been renewed 11 times, with the current HHS Secretary, Xavier Becerra, stating that a public health emergency still exists.[1]

During a public health emergency, the Public Readiness and Emergency Preparedness (PREP) Act has been leveraged to expand the scope of practice for health care practitioners and to employ various countermeasures to address the emergency. Utilization of the PREP Act has allowed pharmacists to play a pivotal role in protecting patients against COVID-19. Pharmacists are authorized under PREP Act declarations to order(prescribe) and administer COVID-19 vaccines, tests, and therapeutics. Qualified pharmacy technicians and pharmacy interns are authorized to administer COVID-19 vaccines, tests, and COVID-19 therapeutics, as appropriate and in accordance with state laws.[2,3]

Community pharmacists started dispensing oral antivirals for the treatment of COVID-19, nirmatrelvir/ritonavir and molnupiravir, in December 2021.[4,5] On July 6, 2022, the U.S. Food and Drug Administration (FDA) updated the Emergency Use Authorization (EUA) for nirmatrelvir/ritonavir to authorize state-licensed pharmacists to prescribe the medication with certain limitations. [6]The federal government had already authorized pharmacists to order and administer COVID-19 therapeutics in the Ninth Amendment to Declaration Under the PREP Act for Medical Countermeasures Against COVID-19.[3] However, pharmacists were not included as authorized prescribers under the conditions in the original FDA EUA for nirmatrelvir/ritonavir. FDA's label change removed this barrier to permit nirmatrelvir/ritonavir to be prescribed by a state-licensed pharmacist if the pharmacist has sufficient information to assess renal and hepatic function and sufficient information to assess for potential drug-drug interactions.[4]

This resource is designed to offer pharmacists a concise and accurate tool for assessing patient eligibility for pharmacist-prescribed nirmatrelvir/ritonavir, including identifying and managing drug interactions. Pearls for implementing this clinical service are also provided. This guide is meant to build on the infrastructure and practices community pharmacists are already employing to contend with COVID-19 and incorporate this new authority to further benefit the public.

Operationalizing COVID-19 Therapeutics Prescribing Services

Community pharmacies are in an excellent position to offer COVID-19 Test to Treat services that include performing COVID-19 testing, and if the test is positive, pharmacist-conducted assessment of the patient for eligibility to be prescribed an oral antiviral. Pharmacies dispensing nirmatrelvir/ritonavir have devised solutions for minimizing the spread of disease, developed ways to verify adequate renal and hepatic function, and identified and collaborated with other health care providers to manage potential drug interactions. Pharmacy workflow shifts have occurred, and other pharmacy staff have taken on new responsibilities to allow additional time for pharmacist counseling and verification.[2] These actions have laid the foundation for the patient assessment for pharmacist-prescribed nirmatrelvir/ritonavir. Figure 1 highlights pearls for implementing treatment services for COVID-19 and Figure 2 shows the roles of pharmacy team members.

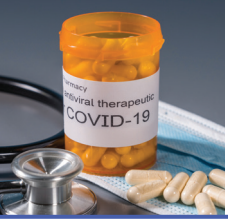

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Figure 1. Pearls for Implementing Pharmacist-Prescribed COVID-19 Therapeutics

- Minimize COVID-19 disease exposure of staff and other patients by offering intake and triage electronically or telephonically and curbside pickup.
- Use online portal to streamline intake of information and facilitate billing.
- Implement procedure for administering or verifying COVID-19 test results.
- Collect medication lists and objective parameters (e.g., height, weight, pulse oximetry [SpO2], blood pressure) electronically to assess for eligibility and potential drug-drug interactions.
- Collect labs within the last 12 months to assess renal and hepatic function.
- Minimize patient wait time at the pharmacy when collaboration with other health care professionals is needed.
- Institute processes for documentation and patient follow-up.
- Consider space, staffing, and pharmacist time when determining pricing.
- Use pharmacy extenders (e.g., pharmacy interns, technicians, ancillary staff) when able.

Figure 2. Pharmacy Team Roles[4,7]

Pharmacists

- All tasks of a pharmacy intern
- Obtain and interpret labs[a]
- Assess severity of disease and refer patients as necessary
- Identify and mitigate drug interactions
- Collaborate with other health care providers to alter medication regimens
- Prescribe nirmatrelvir/ritonavir
- Final verification of prescription
- Document patient services
- Provide patient counseling

Pharmacy Interns

- All tasks of a pharmacy technician
- Communicate with other healthcare personnel to obtain labs or medication lists or clarify prescriptions[a]
- Counsel patients on prescription and over-the-counter products[a]

Certified Pharmacy Technicians

- All tasks of ancillary pharmacy staff
- Enter new written or electronic prescriptions
- Fill prescriptions
- Communicate with patient and insurance companies

Ancillary Pharmacy Staff

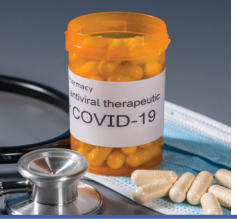
- Develop technology infrastructure for patient screening, consent, and payment
- Verify patients' insurance coverage
- Schedule patient appointments
- Complete transaction at point of sale
- Deliver pharmacy products to patients

[a] Varies from state to state.

Clinical Decision Making

Pharmacists have been making medication recommendations for decades; however, for the first time on a federal level, pharmacists are authorized to initiate medication therapy. With appropriate information and authority, pharmacists are capable of prescribing because they are the medication experts. Many of the same strategies that pharmacists use to verify appropriate therapy prior to dispensing can be used when prescribing nirmatrelvir/ritonavir. Owing to significant drug-drug and drug-disease interactions, there are additional steps pharmacists must perform when prescribing nirmatrelvir/ritonavir.

In accordance with the EUA of nirmatrelvir/ritonavir, pharmacists must obtain the patient's lab results from within the last 12 months to assess renal and hepatic function, obtain a complete medication list to assess potential drug-drug interactions, and determine whether the patient is at high risk for progression to severe COVID-19 disease.[4] While managing drug interactions is a core duty of all pharmacists, it is less common for pharmacists to have access to patient lab results in the community pharmacy setting or determine the severity of disease. Retrieving lab results can be one barrier to access of oral antiviral COVID-19 therapeutics, however it is critical to ensuring safety. In recent years, it has become more commonplace for clinics to have a patient portal where patients can access their past lab results, and patients can retrieve the results electronically or print out this information for the pharmacist. It is important for pharmacists to take a stepwise approach to clinical assessment for patients who may need treatment with nirmatrelvir/ritonavir. Figure 3 provides an algorithm to support pharmacists with clinical decision making.



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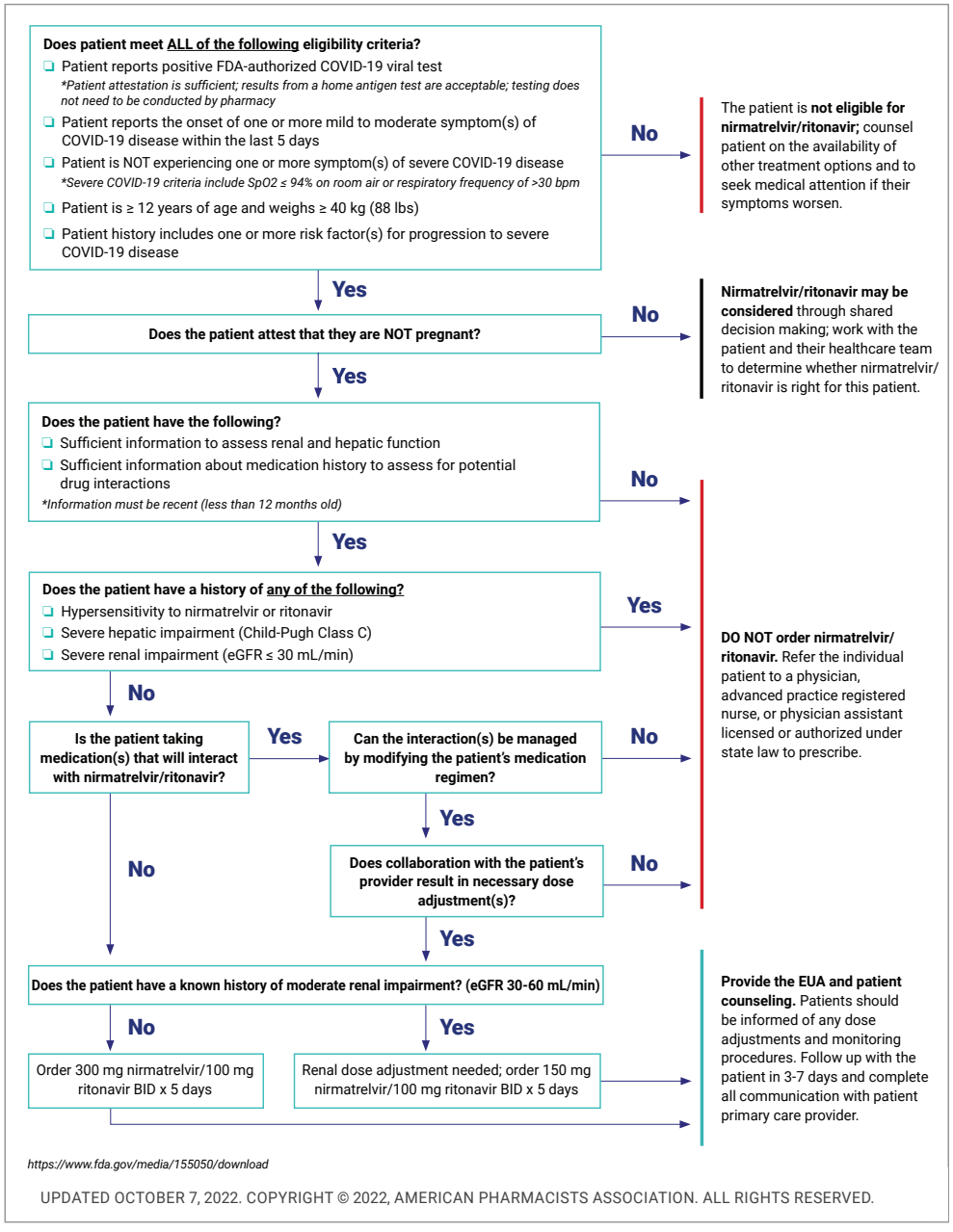
Drug Interactions with Commonly Used Drugs

Approximately 90% of drugs are metabolized by cytochrome P450 (CYP) 1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5. Coadministration of CYP enzyme inhibitors or inducers can alter drug concentrations leading to toxicity and unwanted side effects or failure of the drug due to subtherapeutic levels, respectively.[8] Ritonavir, which is used to treat COVID-19, has potential to impact five of the CYP enzymes that metabolize most drugs. It is a substrate and inhibitor of CYP3A4, a moderate affinity substrate of CYP2D6, and an inducer of CYP1A2, CYP2B6, CYP2C9, and CYP2C19. Nirmatrelvir, the other component of the recommended oral antiviral for treatment of COVID-19, is also a substrate of CYP3A4.[4]

Ritonavir can also inhibit P-glycoprotein (P-gp) and cause QT corrected (QTc) prolongation. P-gp is an efflux transporter which pumps medications back into the lumen thereby decreasing absorption.[9] Ritonavir can therefore lead to increased drug concentrations of medications typically dispositioned by P-gp. Many of the drugs transported by P-gp are also metabolized by CYP3A4.[9,10] Coadministration with other QTc prolonging drugs can lead to Torsades de Pointes and sudden death. Therefore, concomitant administration of drugs that also prolong the QTc is not advised.[11]

Figure 3. Pharmacist Decision Making Support for Paxlovid (nirmatrelvir/ritonavir)[4]



https://www.fda.gov/media/155050/download

This comprehensive clinical decision support tool can be found here.

CYP3A4 Inhibition

Table 1 lists some of the most commonly used CYP3A4 substrates. When used concomitantly with nirmatrelvir/ritonavir, ritonavir inhibits CYP3A4. As a result, the drug concentration of the concomitant medication increases leading to increased risk of adverse events. When dose adjustments must be made, most drugs can be restarted at their usual dose 3 to 5 days after the final dose of nirmatrelvir/ritonavir.[8,11]

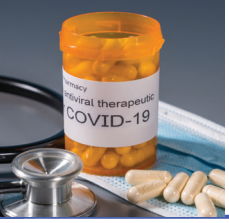


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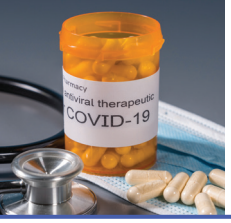
Table 1. Select Clinically Significant CYP3A4 Drug Interactions (Inhibition)[8,11]

Concomitant Medication	Possible Effect	Recommendation During Nirmatrelvir/Ritonavir Treatment
Alpha-1 blockers (alfuzosin, silodosin, tamsulosin)	Hypotension, orthostasis	Hold alpha-1 blocker during coadministration; monitor blood pressure. Tamsulosin—Dose reduction to 0.4 mg/day may be considered.
Antipsychotics (aripiprazole, brexpiprazole)	Confusion, fainting, aggression, tachycardia	Reduce dose by 50%.
Antipsychotics (lurasidone)	Cardiac arrhythmias	Use alternate COVID-19 therapeutic.
Benzodiazepines (alprazolam, chlordiazepoxide, clobazam, clonazepam, diazepam)	Excess sedation, respiratory depression	Consider dose reduction, but do not stop if chronic use. Alprazolam—Reduce dose by 50%.
Calcineurin inhibitors[a] (cyclosporine, tacrolimus)	Acute renal failure, toxicity	Use alternate COVID-19 therapeutic.
Calcium channel blockers (amlodipine, diltiazem, nifedipine, verapamil, felodipine, nicardipine)	Decreased blood pressure	Monitor blood pressure; consider a dose reduction. Amlodipine—Reduce dose by 50% or reduce the dosing interval to every other day.
Colchicine[a]	Inflammation	Consider holding; monitor for signs of toxicity. If there is renal or hepatic impairment, coadministration is contraindicated.
Direct oral anticoagulants (apixaban[a]; edoxaban, dabigatran)	Increased bleeding risk	Dependent on indication: Treatment of atrial fibrillation Reduce dose by 50%. Dabigatran—Reduce dose to 110 mg twice daily. Dabigatran CrCl of 30–50 mL/min—Reduce dose to 75 mg twice daily. Venous /arterial thromboembolism Consider switching to a low-molecular-weight heparin; patients with a low risk could be switched to aspirin on a case by case basis. Monitor for signs of bleeding.
Direct oral anticoagulants (rivaroxaban)	Increased bleeding risk	Use alternate COVID-19 therapeutic.
Opioids (fentanyl)	Respiratory depression	Reduce dose by 50%; monitor carefully for signs of opioid overdose; provide naloxone.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, rosuvastatin, simvastatin)	Increased toxicity and risk of rhabdomyolysis	Hold medication and monitor for signs of rhabdomyolysis. Give the first dose of nirmatrelvir/ritonavir 12 hours after last statin dose and do not restart until 3 days after last dose of nirmatrelvir/ritonavir.
Maraviroc	Hepatotoxicity	Reduce dose and monitor for adverse effects. eGFR >80 mL/min/1.73 m^2 150 mg twice daily. eGFR <80 mL/min/1.73 m^2 reduce dose to 150 mg once daily.
PDE5 inhibitors (avanafil, sildenafil, tadalafil, vardenafil)	Visual abnormalities, hypotension	Dependent on indication: Erectile dysfunction or Raynaud phenomenon Hold during and 3 days after the last dose of nirmatrelvir/ritonavir. Pulmonary edema or pulmonary hypertension Use alternate COVID-19 therapeutic.
Quetiapine	Central nervous system depression and sinus tachycardia	Reduce dose of quetiapine to one-sixth of the original dose during concomitant therapy.

[a] This medication is also affected by P-gp efflux inhibition.

Abbreviations: CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; PDE5, phosphodiesterase type 5; P-gp, P-glycoprotein.



CYP3A4 Induction

Table 2 lists some of the most common strong CYP3A4 inducers. Coadministration of nirmatrelvir/ritonavir with CYP3A4 inducers will reduce nirmatrelvir/ritonavir concentrations leading to therapeutic failure. As induction takes weeks of refraining from the medication before induction subsides, it is not possible to hold the inducer to provide therapy with nirmatrelvir/ritonavir.[8] In this case, it is best to use an alternate therapeutic.[4] Remdesivir is currently recommended as second-line therapy.[4]

Table 2. Select Clinically Significant CYP3A4 Drug Interactions (Induction) [8,11]

Concomitant Medication	Possible Effect	Recommendation During Nirmatrelvir/Ritonavir Treatment
Antiepileptics (carbamazepine, phenobarbital, phenytoin, primidone)	Therapeutic failure	Use alternate COVID-19 therapeutic.
Rifampin	Therapeutic failure	Use alternate COVID-19 therapeutic.
St. John's wort	Therapeutic failure, especially in dose of hyperforin >1 mg daily	Use alternate COVID-19 therapeutic.

Drug Interactions With Other Mechanisms

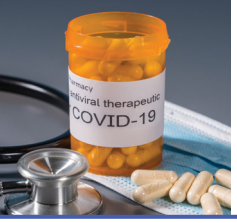
Other drug interactions exist: ritonavir induces CYP1A2, CYP2B6, CYP2C9, and CYP2C19, competitively inhibits CYP2D6, inhibits P-gp, and can prolong the QTc interval.[9,10] Table 3 reviews some of the more common interactions not involving CYP3A4.

Table 3. Select Clinically Significant Drug Interactions (Other Mechanisms)[,10]

Concomitant Medication	Possible Effect	Recommendation During Nirmatrelvir/Ritonavir Treatment
Antiarrhythmic (amiodarone, dronedarone, flecainide, propafenone, quinidine)	Arrhythmias and cardiac arrest	Use alternate COVID-19 therapeutic.
Clozapine	Hematological abnormalities	Use alternate COVID-19 therapeutic.
Digoxin	Cardiac abnormalities	Reduce dose by 30%–50%; dose reduction should be based on treatment indication and patient renal function.
Hormonal contraceptives (ethinyl estradiol)	Contraceptive failure, spotting	Educate on alternate methods of contraception.
Macrolides (clarithromycin[a]; erythromycin)	Nausea and diarrhea, QT prolongation	Dependent on renal function: eGFR >60 mL/min/1.73 m^2 no dose reduction necessary, but cap dose at 1 g a day. eGFR 30–60 mL/min/1.73 m^2 reduce to dose by 50%. eGFR <30 mL/min/1.73 m^2 nirmatrelvir/ritonavir should not be used. Consider switching to a non-interacting macrolide (azithromycin).
Methadone	Withdrawal, decreased effects	No dose adjustment is necessary, but patients should be counseled on possibly experiencing withdrawal symptoms.
Narcotics (oxycodone, hydrocodone, tramadol)	Respiratory depression, therapeutic failure	Monitor for pain relief and toxicity.
Trazodone	Sedation, hypotension, QT prolongation	Reduce dose by 50%.
Warfarin	Increased risk of bleeding or clotting	Carefully monitor INR.

[a] This medication is also affected by P-gp efflux inhibition.

Abbreviations: eGFR, estimated glomerular filtration rate; INR, international normalized ratio; P-gp, P-glycoprotein.



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Helpful Resources

American Pharmacists Association. Prescribing Considerations for COVID-19 Therapeutics [CPE Training]

American Pharmacists Association. Test to Treat for Paxlovid

Centers for Disease Control and Prevention. COVID-19: People With Certain Medical Conditions [Risk Groups for Progression to Severe Disease]

Infectious Diseases Society of America. Management of Drug Interactions with Nirmatrelvir/Ritonavir (Paxlovid): Resource for Clinicians

National Institutes of Health. Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications [Drug Interactions Tool]

National Institutes of Health. Therapeutic Management of Non-hospitalized Adults With COVID-19

Ontario COVID-19 Drugs and Biologics Clinical Practice Guidelines Working Group. Nirmatrelvir/Ritonavir (Paxlovid): What Prescribers and Pharmacists Need to Know [Drug Interactions Tool]

University of Liverpool. COVID-19 Drug Interactions [Drug Interactions Tool]

U.S. Food and Drug Administration. Paxlovid Eligibility Screening Checklist Tool for Prescribers

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