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COVID-19 Studios: Navigating Drug-Drug Interactions

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Welcome to ReachMD. This medical industry feature is titled “COVID-19 Studios: Navigating Drug-Drug Interactions”. This podcast is for US healthcare professionals only and is intended to be listened to as it was originally produced by Pfizer. This podcast has been paid for by Pfizer. Dr. Balile and Dr. Morgan have been compensated for their participation. Dr. Griffin and Dr. Racaniello, however, have not been compensated for their participation in this podcast. This promotional podcast is not certified for continuing medical education.

Dr. Griffin:
Hello everyone, and welcome to the second episode of “COVID-19 Studios”- a series of podcast episodes, where we will discuss the facts and science behind PAXLOVID, an FDA-approved prescription treatment option for COVID-19!

I’m Dr. Daniel Griffin, an Infectious Disease physician-scientist at Columbia University Medical Center.

Dr. Racaniello:
And I’m Dr Vincent Racaniello, a virologist in the Department of Microbiology and Immunology at Columbia University.

The goal of the “COVID-19 Studios” series is to address hot topics that have been top-of-mind within the healthcare professional community about PAXLOVID, a combination of nirmatrelvir and ritonavir, which is an FDA-approved prescription oral treatment option for adult patients with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death.[1]

We hope you caught our exciting first episode, “Decoding an Authorized Prescription Treatment Option”, which addressed 10 facts we believe healthcare professionals will want to know about PAXLOVID. Please note that the first episode was released while PAXLOVID was only available under Emergency Use Authorization.

Dr. Griffin:
Vincent and I have partnered with Pfizer in the creation of this podcast.

And we believe it is important for you to know how to determine whether PAXLOVID is appropriate for your adult patients. Drug-drug interactions can occur between PAXLOVID and concomitant medications your patient is taking, and interactions with certain medications may lead to serious adverse reactions.[1] We encourage you to continue listening to understand which of these drug-drug interactions, these DDIs, can be managed by increased monitoring, adjusting the dose of the concomitant medication, or temporarily withholding the concomitant medication.[1]

And today, we have two special guests in our COVID-19 Studios to help us explore our topic, which is how to consider and navigate the potential drug-drug interactions between PAXLOVID and those concomitant medications when developing your treatment plans. So let me please welcome Dr. Jayne Morgan, a cardiologist from Atlanta, Georgia, and Dr. Samir Balile, a clinical pharmacist for a large pharmacy chain.

Dr. Morgan:
Thank you for having us, Daniel and Vincent! To quickly introduce myself, I’m Dr. Jayne Morgan. I’m a Cardiologist and Healthcare Educator. I re-focused my career during the COVID pandemic on health information and health literacy and in fact, led the COVID Task Force for my institution. Prior to this role, I led research and clinical trials at a large metropolitan medical center. I’ll pass it over to Samir to introduce himself.

Dr. Balile:
Thank you, Dr. Morgan. I'm Dr. Samir Balile. I am a clinical programs manager for a community pharmacy chain with a network of over 400 pharmacists. Prior to my current role, I served as a community pharmacist in the DC area for several years. It has been an eventful time dealing in the COVID-19 space and helping support my community pharmacists on how to handle and to communicate about drug-drug interactions, and to help safely prescribe and dispense PAXLOVID to eligible patients.

While not all DDIs can be managed, I hope that we can increase listeners' confidence in developing treatment plans and managing potential DDIs when possible.[1]

Dr. Morgan:
Exactly, Samir. We'd also like to remind everyone that while the public health emergency is over, COVID-19 is not and continues to be dangerous.[2] It is important that we not let out guards down. Healthcare professionals may perceive the new COVID-19 variants to be much milder – similar to a common cold – and as a result, physicians are less inclined to treat with antivirals.

Dr. Griffin:
Exactly, and it's important that we dispel these misconceptions. So thank you both for being here! Your experience on the frontlines and managing these DDIs first-hand will definitely enrich our discussion.

Just a quick recap of the indication before we dive into today's topic—PAXLOVID is indicated for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.[1] PAXLOVID is not approved for use as pre-exposure or post-exposure prophylaxis for the prevention of COVID-19.[1]

Dr. Racaniello:
How do we know that PAXLOVID works? In the pivotal EPIC-HR trial, PAXLOVID reduced the risk of COVID-19–related hospitalization or death from any cause in unvaccinated adult patients by 86% through Day 28 when administered within 5 days of symptom onset, with 9 COVID-19–related hospitalizations or deaths from any cause in the PAXLOVID group versus 64 in the placebo arm.[1]

Dr. Griffin:
So we know PAXLOVID works. We have compelling evidence that it works. But how do we manage this safely? So let's discuss PAXLOVID's boxed warning, having to do with the potential for drug interactions when co-administering PAXLOVID with certain other medications. The concomitant use of a strong CYP3A inhibitor like PAXLOVID and certain other drugs may lead to greater exposure of the concomitant medications, resulting in potentially severe, life-threatening, or fatal events.[1] The potential for drug interactions must be considered before and during treatment, so it is important to review all medications taken by the patient to assess potential drug-drug interactions with PAXLOVID.[1]

Dr. Balile:
It is also important to point out that, other than medications that are contraindicated with PAXLOVID, many common medications with potential drug-drug interactions can be managed by increased monitoring for potential adverse events to concomitant medication, adjusting the dose of the concomitant medication, or temporarily withholding the concomitant medication.[1,3] Before prescribing, consider the benefit of PAXLOVID treatment in reducing hospitalization and death, and whether the risk of potential drug-drug interactions for an individual patient can be appropriately managed.[1]

Dr. Morgan:
Exactly Samir. In fact, according to the NIH, drug interactions that can be appropriately managed should not prevent clinicians from prescribing PAXLOVID for otherwise appropriate patients.[3]

Dr. Griffin:
So let's remind listeners of the 3 types of contraindications to keep in mind for PAXLOVID.

So first, PAXLOVID is contraindicated in those with a history of clinically significant hypersensitivity reactions to its active ingredients—nirmatrelvir or ritonavir—or any other components of the product.[1]

Second, related to drug-drug interactions, PAXLOVID is contraindicated with drugs that are primarily metabolized by CYP3A for which elevated concentrations are associated with serious and/or life-threatening reactions.[1] These drugs should be discontinued either before starting PAXLOVID treatment or during PAXLOVID treatment, and, according to NIH COVID-19 Treatment Guidelines, some of these medications can be resumed after a specific period of time following PAXLOVID treatment.[1,3]

And third, also related to drug-drug interactions, PAXLOVID is contraindicated with drugs that are strong CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virological response and possible resistance.[1] PAXLOVID cannot be started immediately after discontinuation of strong CYP3A inducers due to their delayed offset.[1]

The full list of contraindicated drugs should be reviewed in the PAXLOVID Prescribing Information, which can be found at PAXLOVID.Pfizerpro.com. To hear the full list of contraindicated medications, stay tuned to the end for full Important Safety Information.

Dr. Racaniello:
Now that we've covered the contraindications, let's remind our audience of the factors that place patients at high risk for progression to severe COVID-19, including hospitalization or death, and for whom PAXLOVID may be appropriate.[1]

Dr. Griffin:
Thanks Vincent! Being able to identify these patients in your practice, clinic, or pharmacy setting is critical. The risk factors can be divided into two main categories: One – age 50 and older and two - certain underlying medical conditions or lifestyle factors such as smoking and physical inactivity.[4]

A patient's risk of progressing to severe COVID-19 may also be increased if they are unvaccinated or not up-to-date on their COVID-19 vaccinations. Additionally, some people from racial and ethnic minority groups are at risk of being disproportionately affected by COVID-19.[4]

Dr. Morgan:
I want to take a moment to elaborate further on this last point. Patients from certain racial and ethnic minority groups—including Black, Hispanic or Latino, and American Indian or Alaska Native populations—may be disproportionately impacted from COVID-19 due to systemic inequities and disparities. These include where they live or work, or because they can't access health care, et cetera.[4] Once infected, people from racial and ethnic minority groups are more likely to be hospitalized, more likely to be admitted to the ICU, and more likely to die from COVID-19 at younger ages.[4,5] It's important that we, as healthcare professionals, acknowledge and work to reduce the health inequities and disparities that patients from certain racial and ethnic groups may face.[4]

Dr. Griffin:
Yes, absolutely, Dr. Morgan. It's crucial for us.

Dr. Morgan:
Going back to the two main categories of risk factors, the 5 most common risk factors for severe COVID-19, according to a study from UT Southwestern Medical Center, are having a history of smoking, obesity, age, chronic kidney disease, and type 2 diabetes.[6] If a patient has even one of these risk factors, they are more likely to get very sick or die from COVID-19 when compared to someone with no high risk factors.[4,6]

Dr. Balile:
Exactly, if a patient has one of these risk factors and is experiencing symptoms of COVID-19, it's critical that they see a healthcare professional for an assessment to determine if PAXLOVID treatment may be appropriate for them.[1,4]

Dr. Griffin:
We also highly recommend consulting the CDC website for the full list of high-risk factors and to revisit it frequently to stay on top of updates.

Dr. Balile:
Because there are a number of medical conditions that increase a patient's risk for severe COVID-19[4], I'd imagine that a number of patients who are eligible for PAXLOVID may be taking concomitant medications. What exactly is the cause of the potential drug-drug interactions between PAXLOVID and certain concomitant medications?

Dr. Racaniello:
That is a great question, Samir! The potential drug-drug interactions are attributed to the ritonavir component.[1] Ritonavir is a strong CYP3A inhibitor that helps to inhibit, or slow, the metabolism and breakdown of nirmatrelvir.[1,7] On the other hand, nirmatrelvir inhibits the activity of the SARS-CoV-2 Main Protease, also called M^{pro} or $3CL^{pro}$, which is a viral protein essential for viral replication.[1,7] Thus, ritonavir helps increase the plasma concentrations of nirmatrelvir, by slowing the metabolism, in order for it to remain active in the body for longer periods of time to help combat SARS-CoV-2.[1,7]

The use of ritonavir to boost plasma concentrations and extend half-lives is not new. Due to its CYP3A inhibition, ritonavir has been used for over 25 years in combination with other therapies, so our audience may be familiar.[7–9]

In the context of PAXLOVID treatment, continuing to take or starting medications that are metabolized by CYP3A may lead to clinically significant adverse reactions. Additionally, medications that induce CYP3A may decrease plasma concentrations of PAXLOVID causing a potential loss of therapeutic effect and possible development of viral resistance.[1] These drug-drug interactions should be carefully assessed[1], which brings us here today on the 2nd episode of COVID-19 Studios — Navigating Drug-Drug Interactions.

Dr. Morgan:
As we discussed earlier, because of the inhibition of CYP3A, certain medications are contraindicated with PAXLOVID due to the potential for serious adverse reactions.[1]

But you may have patients on certain concomitant medications that can be managed through dose adjustment, interruption, and/or increased monitoring to enable appropriate use of PAXLOVID.[1,3] It may take a little extra work upfront to navigate these drug-drug interactions, but it is also important that appropriate patients receive treatment.

As mentioned in the first episode of our series, a group at the CDC found that over 97% of patients who experienced severe COVID-19 outcomes, including admission to the ICU, mechanical ventilation, and death, had at least 1 underlying medical condition placing them at high risk.[10] Many of these patients may be on concomitant medications to manage their medical conditions.

Now as a cardiologist and the COVID task force lead for my institution, we should spend time discussing the interactions with certain lipid-modifying statins and anticoagulants.[1] These potential interactions can be managed in your treatment plan. And we cannot just avoid prescribing PAXLOVID for patients with heart disease who test positive—heart disease is among the most common medical conditions associated with increased risk of severe illness from COVID-19.[3,6]

Dr. Balile:
That's critical here and worth repeating. The drug interactions that can be safely navigated should not prevent use of PAXLOVID.[3] This is where collaboration with other health care providers and your local pharmacists can be leveraged.[3] As a pharmacist, I am always happy to help other HCPs understand and navigate the potential DDIs.

Dr. Racaniello:
This brings us to the second half of our episode focusing on hypothetical patient cases. But before we get to those, let's remind our audience of who we are and who we have with us today. I'm Dr. Vincent Racaniello here with my cohost Dr. Daniel Griffin.

Dr. Griffin:
Thanks Vincent! You're listening to the COVID-19 Studios podcast, where we address hot topics about PAXLOVID that have been top of mind within the healthcare professional community. We're here with 2 special guests, Dr. Samir Balile, a clinical pharmacist based in the DC area, and Dr. Jayne Morgan, a cardiologist based in Atlanta—both of whom have experience in the management of patients with mild-to-moderate COVID-19 with PAXLOVID.

Dr. Morgan:
Thank you, Vincent and Daniel! I'm Dr. Jayne Morgan. And today we're discussing how to navigate the potential DDIs that can occur with PAXLOVID and certain concomitant medications.

Dr. Balile:
That's right, Jayne. So continue listening to understand whether these potential DDIs can be appropriately managed by increasing monitoring, adjusting the dose of the concomitant medication, or temporarily withholding the concomitant medication.[1,3]

Dr. Griffin:
Let's dive in and walk through specific examples of navigating DDIs. We have 4 scenarios lined up for us, each involving drug classes that are commonly prescribed in patients who are at high risk for severe COVID-19.[11] These include statins, anticoagulants, hormonal contraceptives, and antipsychotics.[11] We'll tackle each case by applying what we've learned about PAXLOVID so far with the help of Dr. Morgan and Dr. Balile.

Dr. Racaniello:
We will also be using Table 1 from the PAXLOVID prescribing information and the NIH COVID-19 Treatment Guidelines to aid us in navigating the DDIs we'll encounter. Note that the DDIs covered in this podcast are not a comprehensive list of all the drugs that may interact with PAXLOVID. Please consult other appropriate resources, such as the PAXLOVID prescribing information and prescribing

information for the interacting drug, for comprehensive information on dosing, or for monitoring with concomitant use of a strong CYP3A inhibitor such as ritonavir. And please note that Pfizer has developed other resources, like the PAXLOVID Drug Interactions Pocket Resource and a Drug Interactions Checker, to help HCPs evaluate potential DDIs with PAXLOVID. We can use these tools along with our clinical judgment to help determine whether PAXLOVID is appropriate for our patients.[1,3]

Okay, so what are considerations that can help HCPs develop their treatment plans for patients taking these medications?

Dr. Balile:
So Dr. Morgan, posing the first scenario to you. Let's say a 60-year-old patient walked into your office with positive COVID-19 test results, but only mild symptoms—a sore throat, a runny nose, and a slight cough. His symptoms started a day ago, and although his symptoms are mild, he is concerned because he is overweight and has a history of heart problems, including a heart attack 2 years ago.

Dr. Morgan:
So, I'm hearing 3 risk factors: age, heart disease, and an elevated BMI. Based on that, this patient is a potential candidate for PAXLOVID to prevent his COVID-19 from worsening.[1,4]

Dr. Griffin:
I would agree. And I just want to point out that we don't want to wait-and-see. We don't want to let this window close because PAXLOVID must be started within 5 days of symptom onset.[1]

I want to highlight age as one of the risk factors to consider here. According to the CDC, people 50 years of age or older are at least 25 times more likely to die from COVID-19 than 18 to 29 year-olds.[4]

Dr. Balile:
But, throwing a slight wrench into the story, because of his heart condition, he is currently taking atorvastatin to help maintain his cholesterol and prevent future cardiovascular events.

Dr. Morgan:
Based on Table 1 of the PAXLOVID prescribing information, our treatment strategy would depend on the particular statin being used. In our scenario, the patient is on atorvastatin, so we could consider temporary discontinuation during treatment with PAXLOVID.[1]

The NIH COVID-19 Treatment Guidelines align with this guidance, as they recommend withholding atorvastatin during PAXLOVID treatment and resuming following completion of the 5-day PAXLOVID course.[3] However, if withholding a statin is not clinically appropriate, for example, the patient recently had a heart attack, the Guidelines recommend that the dose of atorvastatin be reduced and continued. Overall, for this example, the situation is manageable.[3]

Dr. Racaniello:
Just out of curiosity, how would these potential interactions be handled in a telehealth situation? Daniel, I know you've had a lot of experience with telehealth. How would DDIs be managed in this setting?

Dr. Griffin:
Yes, that's a good question, Vincent. The process shouldn't differ significantly. So, let's talk through an example of a patient seen via telehealth.

Let's say you have a 48-year-old patient. They have been experiencing cough as well as fever for 3 days now and tested positive for COVID-19. The patient set up a telehealth appointment because their symptoms are worsening. The patient has recently had a heart surgery and has atrial fibrillation, for which they take the DOAC apixaban. Based on the patient's clinical picture, their HCP gave an assessment of mild COVID-19 which can be managed in an outpatient setting via telemedicine, and because of their heart condition, this patient is at high risk for progression to severe COVID-19.[12]

Now, the concomitant usage of apixaban must be considered. Both Table 1 of the PAXLOVID prescribing information and NIH COVID-19 Treatment Guidelines recommend adjusting the dose of apixaban and monitoring for adverse effects.[1,3] Since apixaban is a substrate of both CYP3A4 and P-gp, combined P-gp and strong CYP3A4 inhibitors increase exposure to apixaban and increase the risk of bleeding. The apixaban prescribing information recommends that, for patients receiving 5 milligrams or 10 milligrams of apixaban twice daily, the dose of apixaban should be decreased by 50% when coadministered with drugs with a CYP3A inhibitor like PAXLOVID.[13] For patients receiving apixaban at a dose of 2.5 milligrams twice daily, avoid coadministration with PAXLOVID.[13]

Dr. Griffin:
Now, given the need for monitoring, it is important, whether it be through telehealth or an in-person appointment, that you follow-up with

this patient.[1,3]

Dr. Morgan:
Let's next consider a scenario where the patient seeks help at an urgent care center or emergency room, where there may be limited or no medical history available on file.

Dr. Balile:
Okay, so let's say for example you have a 34-year-old female patient presenting with a sore throat, fever, and malaise since 2 days ago, who has tested positive for COVID-19, with type 2 diabetes.[1,4] Diabetes is a high-risk medical condition that would not be immediately visible to a new healthcare professional. So, when seeing patients who have tested positive, it's important to ask questions and determine whether risk factors for severe disease are present.

Dr. Racaniello:
Continuing with this patient case, this patient is eligible for PAXLOVID[1,4], but the patient is taking concomitant metformin for type 2 diabetes and an oral hormonal contraceptive to prevent pregnancy. Samir, how might this impact their ability to take PAXLOVID?

Dr. Balile:
So the oral contraceptive is the potential issue here. According to Table 1 of the PAXLOVID prescribing information and the NIH COVID-19 treatment guidelines, co-administering contraceptive products that contain ethinyl estradiol with PAXLOVID may result in lower ethinyl estradiol concentrations.[1,3] Counsel the patient to use an additional, non-hormonal method of contraception during the 5 days of PAXLOVID treatment and until one menstrual cycle after stopping PAXLOVID.[1,3]

With regards to the metformin, based on the NIH COVID-19 Treatment Guidelines, use of the metformin can be continued without adjusted dose or increased monitoring.[3]

Dr. Griffin:
You may also have patients that you see regularly who are eligible for PAXLOVID.

Let's say you have a 30-year-old patient you have treated for the past 10 years who is living with bipolar disorder and is physically inactive. This patient has come to you with a 4-day headache and a runny nose, as well as a positive COVID-19 test result. Your patient is at high-risk for severe COVID-19 outcomes because of his mood disorder or mental health condition and lack of physical activity. Thus, this patient is eligible for PAXLOVID.[1,4]

Dr. Balile:
This is an ideal scenario—you've worked with the patient for many years, and you are likely well aware of the medications, like antipsychotics, they are taking.

Dr. Griffin:
Exactly. If the patient is taking quetiapine, for example, you will be able to develop a treatment plan in a timely manner. Please do note that the antipsychotics lurasidone and pimozide are contraindicated with PAXLOVID.[1]

Dr. Balile:
According to Table 1 of the PAXLOVID prescribing information and the NIH COVID-19 Treatment Guidelines, the antipsychotic quetiapine should be continued, as necessary, with a reduced dose and increased monitoring for adverse effects.[1,3]

In addition, the PAXLOVID prescribing information also recommends referring to quetiapine's prescribing information.[1] Quetiapine's PI states that the dose of quetiapine should be reduced to one sixth of the original dose when co-medicated with a potent CYP3A inhibitor, like PAXLOVID.[14] And when PAXLOVID is discontinued, the dose of quetiapine should be increased by 6-fold back to the original dose.[14]

From these patient cases, I think we can all agree that it's important to empower our patients to act, as symptoms may progress quickly for patients at high risk for severe COVID-19,[4,15] but also to take the time to appropriately manage patients who are taking concomitant medications.[1,3]

This process may require collaborating across specialties or an additional time commitment. But neglecting treatment of these patients can be dangerous—as we've noted multiple times, high-risk patients carry significant risk for progression to severe outcomes.[3,4,15]

And I think I can speak for most clinical pharmacists when I say, don't hesitate to reach out to your pharmacy colleagues for help navigating DDIs and managing patients on concomitant medications appropriately.[3]

Dr. Griffin:
Dr. Balile, I'd like to hear about your experience processing PAXLOVID prescriptions—how often do you find yourself supporting primary care physicians or other HCPs in navigating the DDIs associated with PAXLOVID?

Dr. Balile:
Quite often the pharmacists I work with are having to obtain additional information from the patient's prescriber. Many prescribers rely on the recommendations of the pharmacist to guide certain medication dose adjustments or temporary withholding of certain medications that are listed, or sometimes not listed, in the patient's EMR. Thus, interprofessional collaboration is mission critical to ensure the patient obtains the appropriate treatment.

Dr. Griffin:
And if there is hesitancy from the patient, consider combatting it by underscoring the potential for their progression to severe disease.

Dr. Racaniello:
Empower your high-risk patients on concomitant medications to understand their risk and make a plan. As we mentioned earlier, PAXLOVID is an effective oral antiviral for the treatment of adult patients with mild-to-moderate COVID-19 at high risk for progression to severe disease, including hospitalization or death, and drug interactions that can be appropriately managed should not prevent the use of PAXLOVID.[1,3,4]

Dr. Griffin:
Please note that you can find links to the PAXLOVID prescribing information and the NIH COVID-19 Treatment Guidelines on this podcast's episode page. In addition, as mentioned earlier, Pfizer provides the PAXLOVID HCP Drug Interactions Pocket Resource and their own Drug Interaction Checker, links to which can be found on the podcast's episode page. You can also search PAXLOVID.Pfizerpro.com in your browser to navigate to the Prescribing Information for PAXLOVID.

This "COVID-19 Studios" episode is not complete until you listen to the following Important Safety Information, so please ensure you do so.

Dr. Racaniello:
Absolutely Daniel! Please listen to the full Important Safety Information, including the drug interactions with PAXLOVID.

INDICATION & IMPORTANT SAFETY INFORMATION

INDICATION
PAXLOVID is indicated for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

Limitations of Use
PAXLOVID is not approved for use as pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

IMPORTANT SAFETY INFORMATION
WARNING: SIGNIFICANT DRUG INTERACTIONS WITH PAXLOVID

- **PAXLOVID includes ritonavir, a strong CYP3A inhibitor, which may lead to greater exposure of certain concomitant medications, resulting in potentially severe, life-threatening, and/or fatal events**
- **Prior to prescribing PAXLOVID: 1) Review all medications taken by the patient to assess for potential drug-drug interactions with a strong CYP3A inhibitor like PAXLOVID and 2) Determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring**
- **Consider the benefit of PAXLOVID treatment in reducing hospitalization and death, and whether the risk of potential drug-drug interactions for an individual patient can be appropriately managed**

PAXLOVID is **contraindicated in patients with a history of clinically significant hypersensitivity reactions** (eg, toxic epidermal necrolysis or Stevens-Johnson syndrome) to its active ingredients (nirmatrelvir or ritonavir) or any other components of the product. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue PAXLOVID and initiate appropriate medications and/or supportive care.

PAXLOVID is **contraindicated with drugs that are primarily metabolized by CYP3A and for which elevated concentrations are associated with serious and/or life-threatening reactions and drugs that are strong CYP3A inducers where significantly reduced**

nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. There are certain other drugs for which concomitant use with PAXLOVID should be avoided and/or dose adjustment, interruption, or therapeutic monitoring is recommended. Drugs listed here are a guide and not considered a comprehensive list of all drugs that may be contraindicated with PAXLOVID. The healthcare provider should consult other appropriate resources such as the prescribing information for the interacting drug for comprehensive information on dosing or monitoring with concomitant use of a strong CYP3A inhibitor like PAXLOVID.

Drugs that are primarily metabolized by CYP3A for which elevated concentrations are associated with serious and/or life-threatening reactions:

- Alpha 1-adrenoreceptor antagonist: alfuzosin
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anti-gout: colchicine (in patients with renal and/or hepatic impairment)
- Antipsychotics: lurasidone, pimozide
- Benign prostatic hyperplasia agents: silodosin
- Cardiovascular agents: eplerenone, ivabradine
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin (these drugs can be temporarily discontinued to allow PAXLOVID use)
- Immunosuppressants: voclosporin
- Microsomal triglyceride transfer protein inhibitor: lomitapide
- Migraine medications: eletriptan, ubrogepant
- Mineralocorticoid receptor antagonists: finerenone
- Opioid antagonists: naloxegol
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension
- Sedative/hypnotics: triazolam, oral midazolam
- Serotonin receptor 1A agonist/serotonin receptor 2A antagonist: flibanserin
- Vasopressin receptor antagonists: tolvaptan

Drugs that are strong CYP3A inducers: PAXLOVID cannot be started immediately after discontinuation of any of the following medications due to the delayed offset of the recently discontinued CYP3A inducer:

- Anticancer drugs: apalutamide
  Anticonvulsant: carbamazepine, phenobarbital, primidone, phenytoin
- Antimycobacterials: rifampin, rifapentine
- Cystic fibrosis transmembrane conductance regulator potentiators: lumacaftor/ivacaftor
- Herbal Products: St. John's Wort (*hypericum perforatum*)

Risk of Serious Adverse Reactions Due to Drug Interactions: Initiation of PAXLOVID, which contains ritonavir, a strong CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving PAXLOVID, may increase plasma concentrations of medications metabolized by CYP3A. Medications that induce CYP3A may decrease concentrations of PAXLOVID. These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications
- Loss of therapeutic effect of PAXLOVID and possible development of viral resistance

Severe, life-threatening, and/or fatal adverse reactions due to drug interactions have been reported in patients treated with PAXLOVID. The most commonly reported concomitant medications resulting in serious adverse reactions were calcineurin inhibitors (eg, tacrolimus, cyclosporine), followed by calcium channel blockers.

Hepatotoxicity: Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering PAXLOVID to patients with **pre-existing liver diseases, liver enzyme abnormalities, or hepatitis**.

Because nirmatrelvir is coadministered with ritonavir, there may be a **risk of HIV-1 developing resistance to HIV protease inhibitors** in individuals with uncontrolled or undiagnosed HIV-1 infection.

The most common **adverse reactions** in the PAXLOVID group (≥1%) that occurred at a greater frequency than in the placebo group were dysgeusia (5% and <1%, respectively) and diarrhea (3% and 2%, respectively).

The following adverse reactions have been identified during use of PAXLOVID under Emergency Use Authorization:

Immune System Disorders: Anaphylaxis, hypersensitivity reactions
Skin and Subcutaneous Tissue Disorders: Toxic epidermal necrolysis, Stevens-Johnson syndrome
Nervous System Disorders: Headache
Vascular Disorders: Hypertension
Gastrointestinal Disorders: Abdominal pain, nausea, vomiting
General Disorders and Administration Site Conditions: Malaise

PAXLOVID is a strong inhibitor of CYP3A, and an inhibitor of CYP2D6, P-gp, and OATP1B1. Coadministration of PAXLOVID with drugs that are primarily metabolized by CYP3A and CYP2D6 or are transported by P-gp or OATP1B1 may result in increased plasma concentrations of such drugs and increase the risk of adverse events.

Coadministration with other CYP3A substrates may require a dose adjustment or additional monitoring.

Pregnancy: Available data on the use of nirmatrelvir during pregnancy are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Published observational studies on ritonavir use in pregnant women have not identified an increase in the risk of major birth defects. Published studies with ritonavir are insufficient to identify a drug-associated risk of miscarriage. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy.

Lactation: There are no available data on the presence of nirmatrelvir in human or animal milk, the effects on the breastfed infant, or the effects on milk production. A transient decrease in body weight was observed in the nursing offspring of rats administered nirmatrelvir. Limited published data report that ritonavir is present in human milk. There is no information on the effects of ritonavir on the breastfed infant or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PAXLOVID and any potential adverse effects on the breastfed infant from PAXLOVID or from the underlying maternal condition.

Contraception: Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Advise patients using combined hormonal contraceptives to use an effective alternative contraceptive method or an additional barrier method of contraception.

Pediatrics: The optimal dose of PAXLOVID has not been established in pediatric patients.

Systemic exposure of nirmatrelvir increases in renally impaired patients with increase in the severity of renal impairment. No dosage adjustment is recommended in patients with mild renal impairment. **Reduce the dose of PAXLOVID in patients with moderate renal impairment** (eGFR ≥30 to <60 mL/min). **PAXLOVID is not recommended in patients with severe renal impairment** (eGFR <30 mL/min) or in patients with end-stage renal disease (eGFR <15 mL/min).

PAXLOVID is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C).

Please see Full Prescribing Information, including BOXED WARNING and Patient Information, at the URL shown on-screen.

Dr. Griffin:
Thank you, Dr. Balile and Dr. Morgan, for joining us today!

Dr. Balile:
Absolutely!

Dr. Morgan:
My pleasure!

Dr. Griffin:
We hope this episode provided you with additional confidence when managing some potential DDIs. It's critical to know your patients' risk of severe COVID-19 and to have a treatment plan ready—one that assesses whether PAXLOVID is appropriate.

Thanks Vincent! And everyone, be safe.

ReachMD Announcer:
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