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COVID-19 Studios: Decoding An Authorized Rx Treatment Option

ReachMD Announcer:
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Dr. Griffin:
Hello everyone, and welcome to the first episode of "COVID-19 Studios"- a series of three podcast episodes, where we will discuss the facts and science behind an authorized prescription treatment option!

I'm Dr Daniel Griffin, an Infectious Disease physician at Columbia University Medical Center. I'm a physician scientist who has had the honor of traveling the world to treat patients and teach others.

Dr. Racaniello:
I am Dr Vincent Racaniello, Higgins Professor, Department of Microbiology and Immunology at Columbia University. I've been studying and researching viruses for over 40 years and trying to turn on the world about the fascinating field of virology. It's my passion to teach the everyone about my field, and so I'm really excited to be here.

With that said, Daniel and I have partnered with Pfizer in the creation of this podcast, and we agreed not to have any compensation in exchange for our participation.

For those tuning in, we know there's a lot of misinformation out there about COVID-19, and we believe it's important to step up and continue to do what we have done since the start of the pandemic—which is, provide evidence-based updates about an authorized prescription treatment option for COVID-19.

Dr. Griffin:
Exactly Vincent – I mean, this is what we have been doing since the beginning. We are here to combat the misinformation, here to provide evidence-based updates and the goal of this series is to discuss PAXLOVID, a combination of nirmatrelvir and ritonavir, which is an authorized oral treatment option for adults and pediatric patients 12 years of age and older, weighing at least 88 pounds, with a current diagnosis of mild-to-moderate COVID-19 who are at high risk for progression to severe COVID 19, including hospitalization or death.[1]

Dr. Racaniello:
Daniel, I think you agree that this is an exciting time; can you remember when there was nothing to be done about COVID?2 And now we have options.[3] And for this first…

Dr. Griffin:
I remember it, and I wish everyone was aware, so hopefully we're going to be providing that awareness.

Dr. Racaniello:
Well, that's what we're going to do in this first episode, "Decoding an Authorized Prescription Treatment Option", we are going to address 10 facts that we believe healthcare professionals want to know about PAXLOVID, covering topics that include the risk factors that place patients at high risk of severe COVID-19, information about contraindications and drug interactions, the data from the EPIC-HR trial that supported the Emergency Use Authorization, and, how about this Daniel, viral RNA rebound.

Dr. Griffin:
So how did we land on these facts? Well, we have surveyed social media channels, we've consulted our peers, we've talked with patients in our attempt to identify the topics that seem to require the most clarity. So we hope you'll enjoy this, and the next two upcoming podcasts in the series.

But let's get started with the first critical fact that everyone should know: what is the status of PAXLOVID as it stands today?—it was granted authorization for emergency use in December 2021.4 So what exactly does this mean?

Well, PAXLOVID is not approved but has been authorized for emergency use by the FDA under what is called an Emergency Use Authorization, or EUA, for the treatment of adults and pediatric patients, who are, these are critical to remember, 12 years of age and older and weigh at least 88 pounds, also important with a current diagnosis of mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death.[1]

The emergency use of PAXLOVID is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, unless the declaration is terminated or authorization revoked sooner.[1]

Now, important also is PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19, is not authorized for use as pre-exposure or post-exposure prophylaxis for prevention of COVID-19, and is not authorized, not authorized, for use longer than 5 consecutive days.[1]

Now, the EUA was supported by an interim analysis of the EPIC-HR trial, which we will discuss later in detail in this episode.[1,4]

Um, but I do want to say, for more information on the authorized use for PAXLOVID, please see the Fact Sheet for Healthcare Providers, the Fact Sheet for Patients, Parents, and Caregivers, and the FDA Emergency Use Authorization Letter at PaxlovidHCP.com. Now, a link to this site can also be found in the "Related" section on the Podcast's episode page.

Dr. Racaniello:
Before we discuss who is a candidate for PAXLOVID, let's first discuss the contraindications to help you identify patients for whom PAXLOVID is not appropriate. This brings us to fact number two: there are 3 types of contraindications with PAXLOVID you should be aware of.[1]

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

Second, PAXLOVID is contraindicated with drugs that are highly dependent on CYP3A for clearance, where elevated concentrations are associated with serious and/or life-threatening events.[1] You should review this list by listening to the full Important Safety Information at the end of this podcast, or by referring to the PAXLOVID HCP Fact Sheet which can be found at PaxlovidHCP.com.

Lastly, PAXLOVID is also contraindicated with potent CYP3A inducers where significantly reduced plasma concentrations of nirmatrelvir or ritonavir may be associated with the potential for loss of virologic response and possible resistance.[1] The list of contraindicated drugs within this category should be reviewed in the PAXLOVID HCP Fact Sheet, which can be found at PaxlovidHCP.com. To hear the full list of contraindicated medications, stay tuned to the end for full Important Safety Information.

Dr. Griffin:
Before we move on, I believe it's key that healthcare providers not turn away from prescribing PAXLOVID to appropriate patients. Sure, there may be patients who may not be appropriate, but let's not neglect other patients who may be able to benefit from reducing their risk of severe COVID-19 outcomes.

Dr. Racaniello:
As a reminder, patients who are at high risk for progression to severe COVID-19, including hospitalization or death, may be candidates for PAXLOVID.[1] But what does being high risk mean?

Dr. Griffin:
Thanks Vincent. This segues nicely into our third important fact: know your patient's risk, as not treating patients at high risk for severe COVID-19 may lead to progression of mild-to-moderate symptoms to severe illness.

Some patients are at higher risk of developing severe outcomes of COVID-19, which include hospitalization or death, even if their initial symptoms are mild.[5,6] Not treating patients at high risk within 5 days of symptom onset may rapidly lead to severe COVID-19 outcomes,

such as hospitalization or death.[1,5,6]

Now Vincent, can you tell me how healthcare providers can identify patients at high risk for severe COVID-19?

Dr. Racaniello:
Great question, Daniel. Taking this first step of being able to identify these patients in your practice, clinic, or pharmacy setting is critical. The risk factors can be divided into three main categories: one – age 50 and older, two - certain medical conditions, and three - racial, ethnic, and socioeconomic disparities.[6]

Additionally, being unvaccinated or not being up to date on COVID-19 vaccinations also increases the risk of severe COVID-19 outcomes.[6]

I believe we can easily tackle the age 50 and older category. If a patient was born before 1973, they are at high risk.

Age is actually the strongest risk factor—according to the CDC, people 50 years of age or older are at least 25 times more likely to die from COVID than 18 to 29 year-olds.[6]

Dr. Griffin:
Now, let's discuss the high-risk medical conditions. As of today, according to the CDC, there are over 40 underlying medical conditions to be aware of like asthma, cancer, and cystic fibrosis. What I notice is some may be more obvious than others, and the CDC also includes lifestyle factors, such as a history of smoking or physical inactivity, and mental health conditions, such as depression and schizophrenia spectrum disorders.[6]

And these underlying medical conditions really do dramatically impact a patient's likelihood of getting very sick or dying from COVID-19.[6] A group at the CDC reported on a cross-sectional study conducted from March 2020 to March 2021 of 540,667 adult patients with COVID-19.[5] The purpose of this study was to understand the association between underlying conditions and risk of severe COVID-19 illness.[7]

The results showed 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.[7]

Dr. Racaniello:
That's a very strong association and important to remember, as some of these risk factors may be common and present in patients a healthcare provider encounters every day.[6,8]

Dr. Griffin:
Exactly, Vincent. In fact, the top 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.[8]

Let's move on to the third category: Patients who face racial, ethnic, and socioeconomic disparities are also at increased risk of developing severe illness from COVID-19.[6] This may be due to where they live or work, or because they can't access health care.[6] As healthcare providers, it is so important to recognize this, so that we can strive to ensure all patients receive equitable care.

Dr. Racaniello:
Do your best to commit these high-risk categories to memory, similar to how healthcare providers track the risk factors for other diseases, like stroke, heart disease, or cancer.

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

Dr. Griffin:
So, Vincent, we know COVID-19 is complex. Now that we know which high-risk patients may be appropriate for treatment, can you help us understand or "decode" how PAXLOVID works to inhibit the virus?

Dr. Racaniello:
Daniel, you read my mind. This actually brings us nicely to fact number four.

PAXLOVID is a protease inhibitor combination of two components: nirmatrelvir and ritonavir.1 Nirmatrelvir inhibits the activity of the SARS-CoV-2 Main Protease, also called Mpro or 3CLpro, which is a viral protein essential for viral replication.[9,10] Ritonavir, on the other hand, is not active against Mpro; instead, it helps maintain increased plasma concentrations of nirmatrelvir by inhibiting CYP3A, which metabolizes nirmatrelvir.[9,10]

Compared to the viral spike protein which is targeted by monoclonal antibodies, the main protease is more highly conserved across coronaviruses, which may decrease the likelihood of viral resistance to PAXLOVID.[9,10]

So now that we know the mechanism of action of PAXLOVID, Daniel, can you tell me about the study where it was observed to work in patients at high risk for progression to severe disease?

Dr. Griffin:
We'll soon find out in fact number five, which is all about EPIC-HR. EPIC-HR evaluated protease inhibition with PAXLOVID for COVID-19 in high-risk patients.[11,12] In this study, 2,246 symptomatic adults were given either PAXLOVID or placebo to evaluate efficacy and safety.[11,12]

In EPIC-HR, eligible patients had at least 1 high-risk factor for progression to severe COVID-19 and were given PAXLOVID or placebo orally within 5 days of symptom onset.[11,12] The dose of PAXLOVID was 300 mg nirmatrelvir and 100 mg ritonavir, and both PAXLOVID and placebo were given twice a day for 5 days.[11,12]

Before we go any further, we'll take a pause to highlight the limitations to EPIC-HR. To start, it was a single randomized clinical trial and no vaccinated patients were included.[1,11,12] However, about 50% of participants were seropositive for SARS-CoV-2 antibodies at baseline suggesting that these participants had some pre-existing immunity.[9,10] Another limitation is that the EUA is based on interim EPIC-HR data, and the complete EPIC-HR trial results are under review by the FDA.[1]

A final limitation is that the CDC high-risk criteria differ from the EPIC-HR inclusion criteria for risk factors.[1,6,12]

Dr. Racaniello:
But, Daniel, it's important to note that, despite the differing criteria used in the trial, the FDA granted emergency use authorization for PAXLOVID in patients at high risk for severe COVID-19, as defined by the CDC.[1] And with this background, let's move on to the results.

Dr. Griffin:
This leads us to fact to number five: EPIC-HR met its primary endpoints. PAXLOVID reduced the risk of COVID-19–related hospitalization and death from any cause by up to 86% when these high-risk patients were treated within 5 days of symptom onset, with 9 COVID-19–related hospitalizations or deaths in the PAXLOVID group versus 66 in the placebo arm.[12]

And, when patients were treated within 3 days of symptom onset, PAXLOVID reduced risk of COVID-19–related hospitalization and death from any cause by up to 89%, with 3 COVID-19–related hospitalizations or deaths in the PAXLOVID group versus 27 in the placebo arm.[11,12]

Dr. Racaniello:
I would imagine, Daniel, that some patients at high risk for severe disease may decide to wait and see whether their mild-to-moderate symptoms worsen before starting treatment; however, based on the results from that trial, it's important to start PAXLOVID within 5 days of symptom onset.[6,11,12]

Dr. Griffin:
Indeed. In accordance with the HCP Fact Sheet, healthcare providers should initiate PAXLOVID treatment as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset for appropriate patients.[1]

Let's balance the efficacy results with safety, which brings us to fact number six: similar rates of adverse events were observed between the PAXLOVID and the placebo groups, except for dysgeusia, or altered taste.[11,12]

Adverse events in the PAXLOVID group that occurred at a greater frequency, defined by a greater than or equal to 5 subject difference, than in the placebo group were dysgeusia at 6% versus less than 1%, diarrhea at 3% versus 2%, and hypertension and myalgia, each both reporting 1% versus less than 1%.[1,11,12]

In addition, discontinuation rates due to adverse events were 2.1% in the PAXLOVID group and 4.2% with placebo.[11,12]

Dr. Racaniello:
Thank you, Daniel! I think that was an excellent summary of the clinical data that'll be informative for our listeners.

Dr. Griffin:
Before we "decode" arguably our two most debated topics, drug interactions and the myth and misinformation around viral RNA rebound,

let's do a quick recap of the facts we've discussed thus far. Want to tag-team this, Vincent?

Dr. Racaniello:
You bet Daniel, I'll start – number one, PAXLOVID was granted emergency use authorization in December 2021.[4]

Number two, be aware of the 3 types of contraindications for PAXLOVID to help identify appropriate patients for PAXLOVID.[1]

Dr. Griffin:
Hey, I think you took more than one! So let me jump in with three, know your patients' risk factors and refer to the CDC's list.[6]

And four, PAXLOVID is a protease inhibitor that targets the highly conserved SARS-CoV-2 protease, Mpro.[9-11]

Dr. Racaniello:
Alright I'll take five, that's a famous jazz piece, isn't it? In the EPIC-HR trial, PAXLOVID reduced the risk of severe outcomes in high-risk patients by 86% when administered within 5 days post symptom onset.[12] And get that number, Daniel, within 5 days.

Dr. Griffin:
Number six, regarding safety, similar rates of adverse events were observed between the PAXLOVID and placebo groups, with the exception of dysgeusia, that metallic taste, which occurred more frequently in patients treated with PAXLOVID.[11,12]

Dr. Racaniello:
And here's a number for you, Daniel: over nine and a half million patients had been prescribed PAXLOVID in the United States, as of January 2023.[13]

Dr. Griffin:
That is quite an impressive number.

Alright, so we're halfway through the podcast and going to shift gears to decoding drug-drug interactions with PAXLOVID and discuss why potential drug interactions may occur.

Dr. Racaniello:
I know you're going to like this part, Daniel, because you're a big fan of CYP3A I understand.

I am, I am. And that's one of those things – if you mention CYP3A, people just think you're smart. So, everyone listening…

Dr. Racaniello:
It's a good, good word for a cocktail party! Okay, we know that the ritonavir component of PAXLOVID is a strong inhibitor of CYP3A. So, continuing to take or starting new medications that are metabolized by, or that induce, or inhibit CYP3A along with PAXLOVID – that could increase or reduce plasma concentrations of your medications, and that could lead to serious adverse events.[1] So, we have to carefully assess these drug-drug interactions.

As we talked about earlier, due to the effect on CYP3A, some medications are contraindicated with PAXLOVID.[1] PAXLOVID is not appropriate for patients taking these contraindicated medications.[1] And you know, Daniel, we get e-mail about that all time, right?

Dr. Griffin:
We do, we do. So, you know, mentioning and knowing about CYP3A will not only make you appear smart at a cocktail party, but it's also going to allow you to save people's lives. So I want to discuss fact number seven—your treatment plan must consider drug-drug interactions and contraindications.

Um, So yes, you may have patients for whom PAXLOVID is not appropriate because of contraindications.[1] Um, You may also have patients on certain concomitant medications that could be adjusted or withheld and allow you to safely use PAXLOVID.[1,14]

Um, So this does get a little sophisticated, but that's fine. As we discussed earlier, not treating appropriate patients at high risk for severe COVID-19 while they have mild-to-moderate disease, that "watch-and-wait", that "hope that they'll be okay", this could end up allowing them to progress to severe COVID-19. They can end up in the hospital, they can actually end up dying.[6] So it may take a little extra work upfront to navigate these drug-drug interactions, but it is also important that appropriate patients receive treatment. Don't let this challenge stand in your way.

There are resources that can help—you can see the HCP Fact Sheet for full information on drug-drug interactions, Pfizer has a Drug Interaction Checker, which can provide guidance on using commonly prescribed drug classes—for example, anticoagulants, including warfarin, those HMG-CoA-reductase inhibitors: statins.[1,15] Links to both of these resources can be found in the "Related" section on the

Podcast's episode page. And we'll be providing additional strategies on how you may manage patients on concomitant medications in an upcoming episode in this series. So stay tuned!

Um, but finally, you can always reach out for help, reach out to your pharmacist, your specialist colleagues, um, to get that help that you might need to manage patients on concomitant medications.

Um, but let's discuss the elephant in the room: viral RNA rebound. Um, you may have heard reports of patients, including those who received the full 5-day course of PAXLOVID treatment and other patients who never even got PAXLOVID, who either have experienced a reemergence of symptoms, a negative test followed by a positive test, or both.[16]

Dr. Racaniello:
And I really wanted to say "the elephant in the room"; I'm very jealous that you got there first. Because we've been hearing about this for a long time, and as you know, these kinds of reports can drive hesitancy from both patients and healthcare providers, so it's important to highlight our fact number eight: which is that viral RNA rebound may in fact be a part of the natural history of SARS-CoV-2 infection in some patients, with or without PAXLOVID treatment, as you have been saying for some time now Daniel.[16]

Dr. Griffin:
Yes, yes. Well, I think you can mention the EPIC-HR study.

Dr. Racaniello:
Let's do that. In this study, post-treatment increases in SARS-CoV-2 RNA shedding levels were observed in a subset of patients who received PAXLOVID. RNA shedding was also observed for placebo recipients, who never got the drug.[1,16] The frequency of detection of post-treatment viral RNA rebound was generally similar among PAXLOVID and placebo recipients, regardless of the rebound definition that was used.[1,16]

And as of this moment, when you and I are talking, Daniel, according to the CDC, limited information currently available from case reports suggests that rebound cases are mild, and few cases of severe disease during rebound have been reported.[16-18]

Dr. Griffin:
Yes, I mean even for those that we haven't convinced, rebound is something we see with and without treatment.[16-18]

And, as of February 2023, the CDC continues to recommend PAXLOVID for appropriate high-risk individuals.[16]

I think that it's important that we continue to, uh, to emphasize this.

Dr. Racaniello:
Finally, for your reference, our listeners, we'll put a link to the CDC's Health Advisory on COVID-19 rebound in the "Related" section on the Podcast's episode page for your reference.

Dr. Griffin:
We've discussed a lot thus far, but we have yet to "decode" dosing for PAXLOVID. For many of you, this may be a refresh but for some, it may be your first time prescribing PAXLOVID.

Fact number nine is that PAXLOVID is available in 2 dose packs: a standard dose pack, which contains 30 tablets divided into 5 daily-dose blister cards, and a reduced dose pack for patients with moderate renal impairment, which contains 20 tablets divided in 5 daily-dose blister cards.[1,19]

The standard dose of PAXLOVID is 300 milligrams of nirmatrelvir, which includes two 150 milligram tablets, and one 100 milligram ritonavir tablet all taken together every 12 hours for 5 consecutive days.[1,19]

Dr. Racaniello:
So to be clear, this is a total of 3 tablets in the morning and another 3 tablets in the evening for 5 days, correct?

Dr. Griffin:
Exactly, and, if it's helpful, all tablets are pre-packaged in blister cards with morning and evening icons, so our patients may follow the course along for the complete 5 days.[19]

Dr. Racaniello:
Daniel, you mentioned that the reduced dose is appropriate for patients with moderate renal impairment. What about for patients with mild or severe renal impairment?

Dr. Griffin:
That's a great question. PAXLOVID is not recommended for patients with severe renal impairment, defined as an estimated glomerular filtration rate, or GFR, of less than 30 milliliters per minute per 1.73 m2.[1]

Patients with mild renal impairment, defined as an estimated GFR of 60 to 89 milliliters per minute, should be prescribed the standard dose.[1,19]

Patients with moderate renal impairment, defined as an estimated GFR of 30 to 59 milliliters per minute, should be prescribed a reduced dose of PAXLOVID, which is one 150 milligram tablet of nirmatrelvir and one 100 milligram tablet of ritonavir taken together every 12 hours for 5 consecutive days.[1,19]

Dr. Racaniello:
So just to confirm, that's a total of 2 tablets in the morning and another 2 tablets in the evening for 5 days, correct?

Dr. Griffin:
Exactly Vincent.

Including renal status on the prescription is important to help the pharmacist dispensing PAXLOVID, so that your patient receives the appropriate dose pack. Providing this, as well the relevant lab reports to confirm the patient's renal status, may help avoid potential delays and call backs at the pharmacy.[1,19]

Dr. Racaniello:
Speaking of the role of pharmacists, Daniel, state-licensed pharmacists may prescribe PAXLOVID under certain conditions. First, they must have sufficient information to assess the patient's renal and hepatic function. This information should be accessed from health records less than a year old or from consultation with a healthcare provider that has an established provider-patient relationship with the patient.[1]

Second, the pharmacist must obtain a comprehensive list of the medications, prescribed and non-prescribed, that the patient is taking in order to assess for potential drug interaction. This information should be accessed from health records, a patient's own reporting of medical history, or from consultation with a healthcare provider that has an established relationship with the patient.[1]

Let's "decode" where to find PAXLOVID. Some high-risk patients may be unsure of where to go to determine if PAXLOVID is right for them, upon the onset of mild-to-moderate symptoms.Inform your patients about fact number ten: that, if appropriate, PAXLOVID may be obtained through their primary care office, urgent care centers, or test-to-treat sites.[20,21]

Approximately a year ago, supply was limited, and I recall many providers rationing PAXLOVID to their patients.[22] Well, today in 2023, it has been well-documented that there should be ample supply of PAXLOVID. The COVID-19 Therapeutics Locator provided by the US Department of Health and Human Services can help you locate available supplies of PAXLOVID and other authorized and approved treatment options.[23]

Dr. Griffin:
Thanks Vincent - we encourage all healthcare providers to bookmark the Therapeutics locator, so that they can direct the prescription to the pharmacy most convenient for the patient.[23]

We also want to remind listeners that, as part of the Emergency Use Authorization, the US Government is making COVID-19 treatments currently available to patients at no charge. Although, other administrative fees may apply.[24]

We are here today because we believe that combating misinformation matters and raising awareness around treatment options is critical. The data support PAXLOVID as a treatment option for appropriate patients with mild-to-moderate COVID-19 at high risk for developing severe illness.

Dr. Racaniello:
And don't forget, there are several links available to support this episode on "Decoding an Authorized Prescription Treatment Option". Please see the "Related" section on the Podcast's episode page for these resources, which include: 1. a link to the PAXLOVID HCP website, where you can view the EUA Facts Sheets for Healthcare Professionals and Patients, Parents, and Caregivers; 2. a link to Pfizer Drug Interaction Checker, 3. a link to CDC's Health Advisory on COVID-19 Rebound, and 4. a link to the FDA's EUA Letter. And, for a transcript of this podcast, please see the media menu bar on the Podcast's episode page.

We hope this information enables you to understand or "decode" when and how to use PAXLOVID appropriately. It's critical to know

your patient's risk status and to have a treatment plan ready for your high-risk patients should they be diagnosed with COVID-19.[6]

Dr. Griffin:
This "COVID-19 Studios" kick-off episode is not complete until you listen to the following Important Safety Information, so if you've made it this far, please ensure you do so.

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

Announcer:
IMPORTANT SAFETY INFORMATION

- PAXLOVID is contraindicated in patients with a history of clinically significant hypersensitivity reactions (for example, toxic epidermal necrolysis [TEN] or Stevens-Johnson syndrome) to its active ingredients (nirmatrelvir or ritonavir) or any other components of the product.
- Drugs listed in this section 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 such as ritonavir.
- PAXLOVID is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions:
  - Alpha1-adrenoreceptor antagonist: alfuzosin; Antianginal: ranolazine; Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine; Anti-gout: colchicine; Antipsychotics: lurasidone, pimozide; Benign prostatic hyperplasia agents: silodosin; Cardiovascular agents: eplerenone, ivabradine; Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine ; HMG-CoA reductase inhibitors: lovastatin, simvastatin; 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

- PAXLOVID is contraindicated with drugs that are potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. 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; Cystic fibrosis transmembrane conductance regulator potentiators: lumacaftor/ivacaftor; Antimycobacterials: rifampin; Herbal Products: St. John's Wort (hypericum perforatum)

- There are limited clinical data available for PAXLOVID. Serious and unexpected adverse events may occur that have not been previously reported with PAXLOVID use.
- Initiation of PAXLOVID, a 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. Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of PAXLOVID, respectively. These interactions may lead to:
  - Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications
  - Clinically significant adverse reactions from greater exposures of PAXLOVID
  - Loss of therapeutic effect of PAXLOVID and possible development of viral resistance

- Consult Table 1 of the Fact Sheet for Healthcare Providers for clinically significant drug interactions, including contraindicated drugs. Drugs listed in Table 1 are a guide and not considered a comprehensive list of all possible drugs that may interact with PAXLOVID. Consider the potential for drug interactions prior to and during PAXLOVID therapy; review concomitant medications during PAXLOVID therapy and monitor for the adverse reactions associated with the concomitant medications.
- Anaphylaxis and other hypersensitivity reactions have been reported with PAXLOVID. Cases of Toxic Epidermal Necrolysis and Stevens-Johnson syndrome have been reported with ritonavir, a component of PAXLOVID (refer to NORVIR prescribing information). If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue

PAXLOVID and initiate appropriate medications and/or supportive care.

- 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 co-administered 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.
- Adverse events in the PAXLOVID group (≥1%) that occurred at a greater frequency (≥5 subject difference) than in the placebo group were dysgeusia (6% and <1%, respectively), diarrhea (3% and 2%), hypertension (1% and <1%), and myalgia (1% and <1%). The proportions of subjects who discontinued treatment due to an adverse event were 2% in the PAXLOVID group and 4% in the placebo group.
- The following adverse reactions have been identified during post-authorization use of PAXLOVID. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
  - *Immune System Disorders*: Anaphylaxis, hypersensitivity reactions
  - *Gastrointestinal Disorders*: Abdominal pain, nausea
  - *General Disorders and Administration Site Conditions*: Malaise

- The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events and medication errors potentially related to PAXLOVID within 7 calendar days from the healthcare provider's awareness of the event.
- Submit adverse event and medication error reports to FDA MedWatch using one of the following methods: online at https://www.fda.gov/medwatch/report.htm; complete and submit a postage-paid FDA Form 3500 and returning by mail or fax; call 1-800-FDA-1088 to request a reporting form.
- In addition, please provide a copy of all FDA MedWatch forms to
- www.pfizersafetyreporting.com, or by fax at 1-866-635-8337 or phone at 1-800-438-1985.
- PAXLOVID is a strong inhibitor of CYP3A and may increase plasma concentrations of drugs that are primarily metabolized by CYP3A. Co-administration of PAXLOVID with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring.
- Nirmatrelvir and ritonavir are CYP3A substrates; therefore, drugs that induce CYP3A may decrease nirmatrelvir and ritonavir plasma concentrations and reduce PAXLOVID therapeutic effect.
- There are no available human data on the use of nirmatrelvir during pregnancy 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.
- 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 reports 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. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.
- 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.
- PAXLOVID is not authorized for use in pediatric patients younger than 12 years of age or weighing less than 88 lb. The safety and effectiveness of PAXLOVID have not been established in pediatric patients. The authorized adult dosing regimen is expected to result in comparable serum exposures of nirmatrelvir and ritonavir in patients 12 years of age and older and weighing at least 88 lb as observed in adults, and adults with similar body weight were included in the trial EPIC-HR.
- Systemic exposure of nirmatrelvir increases in renally impaired patients with increase in the severity of renal impairment. No dosage adjustment is needed in patients with mild renal impairment. In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), reduce the dose of PAXLOVID to 150 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days. Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID. Providers should counsel patients about renal dosing instructions. PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min based on CKD-EPI formula) until more data are available; the appropriate dosage for patients with severe renal impairment has not been determined.

- No dosage adjustment of PAXLOVID is needed for patients with either mild (Child-Pugh Class A)or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with severe hepatic impairment (Child-Pugh Class C); therefore, PAXLOVID is not recommended for use in patients with severe hepatic impairment.
- Please see the Fact Sheet for Healthcare Providers and the Fact Sheet for Patients, Parents, and Caregivers at PaxlovidHCP.com.
- The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product PAXLOVID for the treatment of adults and pediatric patients (12 years of age and older weighing at least 88 lb) with a current diagnosis of mild-to-moderate coronavirus disease 2019 (COVID-19) and who are at high risk for progression to severe COVID 19, including hospitalization or death.
- PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19
- PAXLOVID is not authorized for use as pre-exposure or post-exposure prophylaxis for prevention of COVID-19
- PAXLOVID is not authorized for use for longer than 5 consecutive days
- PAXLOVID may be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs.
- PAXLOVID may also be prescribed for an individual patient by a state-licensed pharmacist under the following conditions:
    - Sufficient information is available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient, to assess renal and hepatic function; and
    - Sufficient information is available, such as through access to health records, patient reporting of medical history, or consultation with a health care provider in an established provider-patient relationship with the individual patient, to obtain a comprehensive list of medications (prescribed and non-prescribed) that the patient is taking to assess for potential drug interaction.

- The state-licensed pharmacist should refer an individual patient for clinical evaluation
- (e.g., telehealth, in-person visit) with a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs, if any of the following apply:
    - Sufficient information is not available to assess renal and hepatic function.
    - Sufficient information is not available to assess for a potential drug interaction.
    - Modification of other medications is needed due to a potential drug interaction.
    - PAXLOVID is not an appropriate therapeutic option based on the authorized Fact Sheet for Healthcare Providers or due to potential drug interactions for which recommended monitoring would not be feasible.

- PAXLOVID is not approved for any use, including for use for the treatment of COVID-19.
- PAXLOVID is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of PAXLOVID under 564(b)(1) of the Food Drug and Cosmetic Act unless the authorization is terminated or revoked sooner.
- Thank you for tuning in. For more information, please refer to the PAXLOVID Fact Sheet for Healthcare Providers or go to PaxlovidHCP.com.

Dr. Racaniello:
Daniel, it was a pleasure speaking with you today! And thank you to our audience for listening and learning! Don’t miss the next episode in the series where we’ll deep dive into the considerations for drug interactions with PAXLOVID.

Dr. Griffin:
Thanks Vincent! And everyone, be safe.

ReachMD Announcer:
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