

## Expert discuss COVID-19 therapeutics and other treatment options

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On Feb. 1, 2022, the AMA hosted the latest webinar in the "COVID-19: What physicians need to know" series.

Hosted by AMA physician leaders, each installment of this COVID-19 webinar series aims to gain fact-based insights from the nation's highest-ranking subject matter experts working to protect the health of the public, particularly during the COVID-19 pandemic.

Gerald E. Harmon, MD, welcomed experts from the U.S. Food and Drug Administration (FDA) to discuss what prescribers need to know about COVID-19 therapeutic drugs, Paxlovid and molnupiravir. Alternative treatment options for high-risk outpatients with mild-moderate COVID-19 were also be discussed.

### Host

- Gerald E. Harmon, MD, AMA president

### Guests

- Stephanie Troy, MD, senior medical officer, Division of Antivirals, Office of Infectious Disease in the Center for Drug Evaluation and Research's Office of New Drugs, FDA
- Aimee Hodowanec, MD, senior medical officer, Division of Antivirals, Office of Infectious Disease in the Center for Drug Evaluation and Research's Office of New Drugs, FDA
- John Farley, MD, MPH, director, Office of Infectious Diseases in the Center for Drug Evaluation and Research's Office of New Drugs, FDA

## Transcript

**Dr. Harmon:** Thank you for joining us this afternoon for the latest in our "What Physicians Need to Know" series about COVID-19 and other important issues in health care. I'm Gerald Harmon, president of the American Medical Association. Today, we're going to delve into the topic of COVID-19 therapeutics recommended usage; it's an important step in our ability to better counsel our patients, answer their questions and provide the most timely and relevant information on how to defeat this virus. For nearly two years now, our country's been battling this deadly pandemic. As of this month we've lost nearly 900,000 lives in the U.S., and more than 5 million around the world.

The Delta variant and now the Omnicron variant have brought renewed pressure on the physician and already taxed health care system, and they've been pretty painful reminders about how just far we still have to go to get this pandemic done control. Despite the widespread availability of vaccines and boosters for adults and children, we're still seeking ways to boost vaccine confidence, to protect more people from severe complications from the virus, and ease distress and strain in our frontline health care workers.

Despite all this, there is some encouraging news; advances and therapeutics create more ways to respond to the coronavirus. Today, I'm delighted to have three leading voices who will share their insights into those therapeutics and how they factor into our ability to respond to COVID-19. I'd like to introduce Dr. John Farley, who will share more about our panelists than our discussion today. John is the director of the Office of Infectious Diseases at the Office of New Drugs at the Center for Drug Evaluation and Research at the FDA. Dr. Farley's office is responsible for the new antiviral and antibacterial drugs, including monoclonal antibodies and small molecule therapeutics. Today, we're going to learn more about some treatment options for high-risk outpatients with mild to moderate COVID-19 from Dr. Farley, and a lot more as we delve in our presentations and later we'll have a few questions and answers. Now I'd like to introduce Dr. Farley, who will share more of about his office's role in emerging COVID-19 therapeutics and our other speakers. Welcome Dr. Farley.

**Dr. Farley:** Thank you, Dr. Harmon, and thanks to all the listeners for all the work that you're doing each and every day, we're going to focus on options of treatment for patients with mild to moderate COVID-19, at high risk of progressing to severe COVID-19, including hospitalization or death. And I'm going to begin with an introduction and overview of injectable treatment options. And then I'll be followed by my colleague, Dr. Stephanie Troy, who will speak on what physicians need to know about Paxlovid. And then, she'll be followed by our colleague, Dr. Aimee Hodowanec, who will speak on what physicians need to know about molnupiravir.

Let's begin our discussion focused on the Omicron variant. The Omicron variant is now estimated to account for 99 of new SARS-CoV-2 infections in the US. This has implications for the monoclonal

antibody therapeutics in particular, because they need to bind to the spike protein of the virus, in order to neutralize the virus. And on your right as data from CDC as of January 15th, and the purple line is the estimate of the proportion of infections in the United States. And the purple bar last week was even more purple. Recently, we've updated our monoclonal antibody fact sheets with virology information concerning Omicron. And the tests that are commonly used in this setting are pseudo virus-like particle neutralization data assays. And what they do is they take the spike protein from the Omicron variant, and express it in a less pathogenic virus. They add the antibody, and measure neutralization. And unfortunately for casirivimab and imdevimab, together known under the brand name of REGEN-COV which many of you I know have been using. There's greater than a thousandfold reduction in susceptibility with Omicron.

For bamlanivimab and etesevimab together, which you've also been using, there's unfortunately greater than a 2,900 fold reduction in susceptibility. Fortunately, for sotrovimab at this time, there is less than a fivefold reduction in susceptibility with is considered to not represent a clinically significant change. So in summary, REGEN-COV and bamlanivimab and Etesevimab administered together are highly unlikely to be active against variants from the Omicron lineage. Whereas, sotrovimab is ex to retain activity against variants from the Omicron lineage. This is just a reminder of sotrovimab and its authorized use. It's authorized for the treatment of mild to moderate COVID-19 in adults and pediatric patients, being 12 years of age and older weighing at least 40 kilograms, who have a positive results of a direct SARS-CoV-2 viral test. So either antigen or PCR, and who are at high risk for progression to severe COVID-19, including hospitalization or death. The dosage is 500 milligrams of sotrovimab, given as soon as possible after positive results of direct SARS-CoV-2 viral testing, and within 10 days of symptom onset. Sotrovimab needs to be diluted and administered as a single IV infusion few over 30 minutes.

I'd like to turn our attention now to Remdesivir. Remdesivir is an improved drug under the trade name VEKLURY. VEKLURY is a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor for the treatment of COVID-19 in adults and pediatric patients. Again, 12 years of age and older, and weighing at least 40 kilograms with positive results of direct SARS-CoV-2 viral testing, who are either hospitalized, a use that many of you are familiar with for some time now, but now an added for patients who are not hospitalized, and have mild to moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death. So a similar use as sotrovimab map. The dosage is a single loading dose of VEKLURY, 200 milligrams on day one via intravenous infusion, followed by once daily maintenance doses of VEKLURY, 100 milligrams from day two via intravenous infusion.

For non-hospitalized patients. The treatment course of should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made and within seven days of symptom onset. And for these patients, the recommended total treatment duration is three days.

Now this approval was based on the study 9012, which some of you are also familiar with; it was published recently. It's a randomized double-blind placebo-control clinical trial that evaluated VEKLURY for a total of three days of intravenously administered therapy, enrolled over 500 adult and eight pediatric patients who were adolescents, non-hospitalized, had mild to moderate COVID-19, were symptomatic for less than seven days had confirmed SARS-CoV-2 infection, and had at least one risk factor for progression to hospitalization. Of note, VEKLURY placebo in this trial was first administered to subjects largely in outpatient facilities, but also in home health care settings or skilled nursing facilities. The primary endpoint was the proportion of subjects with COVID-19 related hospitalizations. That was defined as needing at least 24 hours of acute care, or all cause mortality through day 28. And in terms of these events, they occurred in two or 0.7% of the treated subjects compared to 15 or 5.3% of the subjects randomized to placebo, and that was a statistically significant difference. And there were no deaths observed.

Recently the VEKLURY emergency use authorization for pediatric patients was extended. So we have an approved drug for the adult population, and for adolescents down to age 12, or weighing at least 40 kilograms, and we have an emergency use authorization for pediatric patients. So that drug was authorized for the treatment of certain children, hospitalized or not hospitalized with mild to moderate COVID-19, and at high risk for progression to severe COVID-19. So both a hospital, and a non-hospitalized use similar to the adult approval. And as you can see, we have dosing down to as low as 3.5 kilograms with loading dose of five milligrams per kilogram, and a maintenance dose of 2.5 milligrams per kilogram. So, that's a quick run through of the injectable treatment options. And at this point, I'm going to introduce Dr. Troy, who's going to focus on Paxlovid. Thanks very much.

**Dr. Troy:** Thank you, Dr. Farley, and thank you for me to speak about what physicians need to know about Paxlovid. So, this summarizes what I'll be talking about today, and most of what I'll be talking about is taken from the EUA fact sheet for Paxlovid and the EUA review for Paxlovid and links for those are at the end of my talk. So what is Paxlovid? Paxlovid is the combination product containing nirmatrelvir, co-administered with ritonavir. Nirmatrelvir is a SARS-CoV-2 main protease inhibitor. It blocks the proteolytic cleavage of a polyprotein step of the SARS-CoV-2 replication cycle, which is depicted by the red X. And the figure Ritonavir is a cytochrome P 450 3A4 inhibitor, which is included to increase nirmatrelvir plasma levels. Ritonavir at higher doses used to be used as an HIV protease inhibitor, but Ritonavir has no activity against SARS-CoV-2 on its own.

So Paxlovid is dosed as two, 150 milligram tablets of with 100 milligram tablet of nirmatrelvir, orally twice a day for five days, without regard to food, and as soon as possible after COVID-19 diagnosis, and within five days a symptom onset each carton contains five blister packs, one for each day as depicted on the right. Because dose reduction is needed for moderate renal impairment, each shipment of Paxlovid contains instructions for pharmacists on removing the excess nirmatrelvir natural your tablets when filling prescriptions that specify the moderate renal impairment dose, as well as affixing stickers to the blister packs and carton to cover the dosing instructions with the dosing

instructions for moderate renal impairment.

So Paxlovid that is authorized for the treatment of mild to moderate COVID-19 in adults and pediatric patients, 12 years of age and older weighing at least 40 kilograms with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death now for the conditions which make a patient fall under high risk, we refer to the CDC website for information on medical conditions and factors associated with increased risk for progression to severe COVID-19, and this is updated as data accrue. For the different severities of COVID-19 illness, these are described in the NIH COVID-19 treatment guidelines, but in general, COVID-19 is mild to moderate if the patient has symptomatic SARS-CoV-2 illness, but their oxygen saturation does not drop below 94% on room air. And typically, mild to moderate COVID-19 does not require hospitalization for management. I want to here that the EUA does not specify any particular type of direct SARS-CoV-2 viral test.

For the limitations of authorized use, Paxlovid is not authorized for initiation of treatment and patients requiring hospitalization due to severe or critical COVID-19. Now we deliberately award the limitation in this way to allow use in hospitalized patients in several situations. The first depicted by the footnote is for patients who have mild to moderate COVID-19, and are started on treatment, and then they clinically worsen and require hospitalization due to severe critical COVID-19. And in that situation, the full five day treatment course can be completed per the health care providers discretion. The second scenario is if you have a patient with mild to moderate COVID-19, and they are hospitalized either for unrelated reasons, or because their health care provider wants additional monitoring, for example, for drug interactions, and in that case, the EUA allows for initiation of treatment for mild to moderate COVID-19 in patients in the hospital. Paxlovid is not authorized for use as pre-exposure or post-exposure prophylaxis for prevention of COVID-19, and it's not authorized for use for longer than five consecutive days.

So, data supporting the EUA comes from EPIC-HR, which is a Phase 2/3 double-blind study in over 2000 non-hospitalized symptomatic adults with a laboratory confirmed SARS-CoV-2 infection, who are randomized one-to-one to receive Paxlovid or placebo for five days. The study population was enrolled within five days of cent onset and had at least one risk factor for progression to severe disease. And here I've listed some of those risk factors from the most common to the least common. The population also had no prior COVID-19 vaccine receipt or prior COVID-19 infection. In 98% of SARS-CoV-2 variants identified in EPIC-HR were Delta.

So this slide depicts the efficacy data for the primary endpoint of COVID-19 related hospitalization, or death from any cause through day 28, in the subpopulation who were dosed within five days of symptom onset and who did not receive COVID-19 monoclonal antibody treatment at baseline. And as you can see, eight of the Paxlovid recipients or 0.8% versus 66 of the placebo recipients, or 6.3% met the primary endpoint. And this translates to an absolute risk reduction of 5.6% and a relative risk

reduction of 88% with use of Paxlovid, which is highly statistically significant. You can also see that there were no deaths in the Paxlovid group, compared to 12 deaths in the placebo group. The treatment effect was generally consistent across subgroups, including baseline serology status, meaning that patients who were sero positive for SARS-CoV-2 at baseline, even though overall, they were less likely to be hospitalized or to die, also had a positive treatment effect with Paxlovid.

So the only adverse that were seen in at least 1% of packed recipients with a higher frequency, meaning at least a five subject difference versus placebo recipients dysgeusia, generally described as metallic taste, diarrhea, hypertension, and myalgia. Of note though, the study population excluded children, pregnant woman, individuals with GFR less than 45, individuals with active liver disease, and individuals taking medications that could have clinically significant interactions with Paxlovid. Paxlovid has a lot of drug interactions. Paxlovid is a CYP3 inhibitor, and is also metabolized by CYP3A. This means that Paxlovid may increase plasma concentrations of medications metabolized by CYP3A, which may lead to clinically significant adverse reactions, including fatal events from greater exposures of con medications. In addition, medications that inhibit or induce CYP3A may increase or decrease Paxlovid concentrations, which could lead to loss of therapeutic effect of Paxlovid and possible viral resistance from decreased Paxlovid exposures.

So, as a health care provider, you should inform patients that Paxlovid may interact with some drugs, and is contraindicated for use with some drugs, obtain a complete medication list from your patient, including non-prescription drugs and herbals, check for clinically significant drug interactions, and here I've listed several websites that can help you to do this. And based on the drug interactions decide if Paxlovid use is appropriate versus an alternative authorized treatment. And if appropriate, whether your patient should hold, change or dose reduce other medications while taking Paxlovid, or if additional monitoring may be needed.

So what you should do in specific situations for drug interactions depends not just on characteristics of the interacting medications, such as half life, but also patient-specific factors. For example, depending on the individual patient and condition, some patients may be able to hold a medication with drug interactions while taking Paxlovid, while that may not be safe for other patients. However, we did give specific instructions in the fact sheet where we could, including for the following three scenarios. So if you have a patient who is on a Ritonavir or cobicistat containing HIV antiretroviral regimen, the thought process is that the CYP3A inhibition is already to maximal, both in Paxlovid, and for the HIV regimen. So these patients can take Paxlovid without a dose adjustment, and they can also continue their HIV regimen without change as well.

For patients on simvastatin or lovastatin, which are contraindicated, we recognize that these are very commonly used medications and also, that generally there are not serious clinical consequences from holding these medications for a week. So as simvastatin and lovastatin have short half lives, Paxlovid can be started 12 hours after the last simvastatin or lovastatin dose, if these medications are then held

through about one to two days after completing Paxlovid. For patients on Contra in indicated CYP3A inducers, including phenytoin, phenobarbital, or carbamazepine, these drugs have long half lives, and so cannot be stopped in order to take Paxlovid. Unfortunately, the wash out period is so long that by the time you've held them for long enough, the five day window from symptom onset to treat with Paxlovid would be over. So patients on these drugs should not take Paxlovid, and should instead use alternative authorized or approved treatments for COVID-19.

So, patients with moderate renal impairment need a dose adjustment and Paxlovid is not recommended for patients with severe renal impairment. And in this table, we have the GFRs for the different categories of renal impairment and the different Paxlovid doses, or if it's not recommended, the statement that it's not recommended. So as a health care provider, you should determine the appropriate Paxlovid dose for your patient, specify the numeric dose of each active ingredient nirmatrelvir and retonavir in the Paxlovid prescription for all of your patients, even those with normal renal function, and then counsel patients with moderate renal impairment about renal dosing instructions, and inform them that the blister cards will be altered by the pharmacists to remove unneeded tablets.

So in terms of other specific populations, no dosage adjustment is needed for mild or moderate hepatic impairment, but Paxlovid is not recommended for severe hepatic impairment, due to lack of pharmacokinetic and safety data for a natural, nirmatrelvir or ritonavir. In that population, there are no available clinical data on Paxlovid in pregnancy or with breastfeeding. However, in animal studies reduced fetal body rates were seen at about tenfold higher, no natural exposures than what we'd expect to see with the authorized dose and units. And there were no other adverse developmental effects seen. There are no available clinical data for Paxlovid in children, however, the authorized adult dose is expected to result in comparable serum exposures in patients, 12 years of age and older and weighing at least 40 kilograms, which is the reason that the authorization was expanded to include the adolescent population.

So what about Omicron? So biochemical and cell culture data indicate that nirmatrelvir retains activity against the Omicron variant, so Paxlovid should work against Omicron. However, there are no clinical data yet available from Paxlovid in patients infected with Omicron. EPIC-HR, the trial I discussed that supported the EUA enrolled between in November 5th, 2021, which was before the emergence of Omicron, however, there are several studies underway right now, and so hopefully we will get some data on this in the future.

Other common questions that we've heard about Paxlovid include the following. "So how can you obtain Paxlovid for an eligible patient?" A prescription is needed from a physician advanced practice, registered nurse for physician assistant authorized under state law to prescribe drugs, just like it would be for any prescription drug, and a COVID-19 therapeutic locator website can help identify distribution locations by state. And again, this would vary by state because the states are in charge of distributing

the supply. "Can Paxlovid be taken by individuals who are vaccinated or who receive the monoclonal antibody product Evusheld for preexposure prophylaxis?" Yes, Paxlovid may be used, regardless of COVID-19 vaccination status, or prior monoclonal antibody use under EUA. And likewise Paxlovid use would not impact the timing of future vaccine doses. We do have a small amount of data from EPIC-HR in patients who received monoclonal antibody products with Paxlovid and no safety concerns were identified.

Another comment question is whether Paxlovid can be taken with other authorized COVID-19 treatments. And while the EUA does not prohibit this, there are no data on whether taking an additional treatment with Paxlovid would provide any additional benefit. And we all know about the current short situation with some of these drugs.

So in summary, Paxlovid was authorized in December for the treatment of mild to moderate COVID-19 in adults and pediatric patients, 12 years of age older, and weighing at least 40 kilograms who are at high risk for progression to severe COVID-19. It reduced COVID-19 related hospitalization and death by 88%, when given within five days of symptom onset, without concerning safety findings in the clinical trial EPIC-HR. And key things to remember when prescribing are the multiple drug interactions to reduce dose for moderate renal impairment, and that patients with severe renal impairment, or severe hepatic impairment, currently Paxlovid is not recommended for them. So I will leave you here with some helpful links and then I will pass off to my colleague, Dr. Hodowanec, thank you.

**Dr. Hodowanec:** So thank you, Dr. Troy, and thank you to the organizers for giving me the opportunity to be here with you this afternoon. I'm going to be discussing the molnupiravir EUA, and what physicians need to know. This provides an overview of the content, I will be presenting. The majority of the content that I will be going over can be found in the back sheet for the molnupiravir EUA, and I will be pointing out different ways for patients and for health care providers to access those fact sheets throughout my talk. So how does molnupiravir work? Molnupiravir is a nucleoside analog that inhibits SARS-CoV-2 replication by viral mutagenesis. Molnupiravir under EUA is authorized for the treatment of mild to moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, or at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate. And here you'll find a link to the CDC website, which provides additional details on what may make a person high risk for severe COVID-19. And then here is a link to the FDA website where you can access the molnupiravir fact sheet for health care providers.

There are numerous limitations of the authorized use. Specifically, molnupiravir is not authorized for use in patients who are less than 18 years of age. Molnupiravir is not authorized for the initiation of treatment and patients requiring hospitalization due to COVID-19. And this is because the benefit of treatment with molnupiravir has not been observed in subjects when treatment was initiated after hospitalization for COVID-19, however, should a patient require hospitalization after starting treatment



with molnupiravir, the patient may complete the full five day treatment course, per the health care provider's discretion. Molnupiravir is also not authorized for use for longer than five consecutive days, or for pre or post-exposure prophylaxis for the prevention of COVID-19.

The authorized molnupiravir dosage is 800 milligrams taken orally every 12 hours for five days with or without food. VIR comes in 200 milligram capsules, so patients need to take four capsules twice daily. It should be started as soon as possible after a diagnosis of COVID-19 has been made, and within five days of symptom onset. Completion of the whole five day treatment course and continued isolation in accordance with public health recommendations are both important to maximize viral clearance, and to minimize transmission of SARS-CoV-2. To here, you can see I've included an image of the container label molnupiravir one dispensed under EUA, and wanted to point out that the label does contain this QR code that patients and pharmacists can use to link to the website where again, they can access both the patient fact sheets, as well as the health care provider fact sheets.

The data in support of the molnupiravir EUA come from trial P002 for the MOVE-OUT study. And this was a Phase 2/3 randomized controlled double-blind trial in non-hospitalized adults with COVID-19. And in the top portion here, I show the study schema for the part one or Phase 2 portion of the trial, which was a dose ranging study. And then down here on the bottom is the part two or Phase 3 portion of the study, and this is really where the data in support of the EUA came from is from this Phase 3 portion. And in this Phase 3 portion, a total of 1,550 participants were randomized one-to-one to receive either molnupiravir 800 milligrams to 12 or placebo to 12 for five days. And there was a planned interim analysis conducted when approximately 50% of the population reached day 29. The primary endpoint for this trial is the percentage of participants who were hospitalized or died through day 29 due to any cause.

Here we have a listing of some of the key eligibility criteria for trial P002. Outpatient adults with mild or moderate COVID-19 were eligible if they had laboratory confirmed SARS-CoV-2 infection, with sample collection, as well as onset of symptoms within five days of randomization. All participants in the phase three portion of this trial were at increased risk versus severe illness from COVID-19, and the specific risk factors as defined in the protocol are listed here. SARS-CoV-2 vaccines were prohibited anytime prior to randomization, and through day 29, and pregnant individuals were excluded and contraception was required.

Here, we show the efficacy results for trial P002. As I mentioned, the primary endpoint was all cause hospitalization or death through day 29. 6.8% of molnupiravir participants compared to 9.7% of placebo participants met this endpoint for an adjusted risk difference of 3%, and this equates to an adjusted relative risk reduction of 30%. And then, if we look just at the mortality component of that endpoint, you can see that there were nine deaths among placebo participants, compared to one death amongst molnupiravir participants. Again, these are the results of the whole Phase 3 randomized population. The results of the interim analysis are presented here, and show an adjusted

risk difference of 6.8%.

Here, we have various subgroup efficacy analyses, and a couple things I wanted to point out on this slide are that in certain subgroups, mainly those with diabetes, as well as those with a positive anti-SARS-CoV-2 antibody at baseline. There was no apparent treatment benefit with molnupiravir, however, for most other subgroups, the findings tended to favor molnupiravir, though it is worth noting that many of these subgroups were quite small and all of these results are considered exploratory. In terms of safety, molnupiravir was generally very well tolerated in trial P002. Here we display the adverse reactions that occurred in at least 1% of participants receiving molnupiravir. The only events that reached this threshold were diarrhea, nausea, and dizziness, and as you can see, the rate of each of these was the same in the molnupiravir group as the placebo group.

So, what do physicians really need to know as they're prescribing, or thinking about prescribing molnupiravir? Molnupiravir is not authorized for use in patients less than 18 years of age. And this is because animal findings show that molnupiravir may affect bone and cartilage growth, which is something that could be particularly relevant to pediatric patients. molnupiravir may be used regardless of COVID-19 vaccination status. Breastfeeding is not recommended during treatment with molnupiravir, or for four days after the final dose. No drug interactions have been identified based on the limited available data, and no dosage adjustment is recommended in patients with any degree of renal or hepatic impairment.

There are some unique considerations regarding the potential use of molnupiravir during pregnancy. First and foremost, molnupiravir is not recommended for use during pregnancy, and this is because based on animal data, molnupiravir may cause fetal harm when administered pregnant individuals. However, if a health care provider determines that the benefits of molnupiravir outweigh the risks for an individual pregnant patient, they must first counsel the pregnant patient regarding the known and potential benefits, and potential risks of molnupiravir use during pregnancy. They must also document that the patient has been made aware of these potential benefits and potential risks, and then lastly make the individual aware of the existence of a pregnancy surveillance program. So if the patient agrees to participate in the pregnancy surveillance program, and allows the prescribing health care provider to disclose their patient specific information to Merck, then the prescriber must provide the patient's name and contact information to Merck, either via this 800 number, or electronically through the website with the link shown here.

Now, there are numerous prescriber requirements beyond those that I just reviewed for use in pregnancy. And to make sure that prescribers are aware of these numerous requirements, they are all included in a box near the top of the fact sheet for health care providers, and I will summarize them here. Prescribers must provide an electronic or hard copy of the patient fact sheet, and document that the patient has received a copy of the fact sheet. They must review the information contained within the patient fact sheet with the patient and counsel the patient on the known and potential benefits, and

risks of molnupiravir. Prescribers must also report all medication errors, and serious adverse events that are related to molnupiravir within seven calendar days from the health care provider's awareness of the event. And again, I've provided a link for electronic submission of these reports, as well as an 800 number.

The prescriber must also assess whether an individual or childbearing potential is pregnant or not. This does not necessarily mean that all patients of childbearing potential must undergo pregnancy testing. So pregnancy status does not need to be confirmed in patients who have undergone permanent sterilization, are currently using an intrauterine system, or contraceptive implant, or in whom pregnancy is not possible. However, in all other patients, if the patient is having regular menstrual cycles, using a reliable of contraception correctly and consistently, or if they've had a negative pregnancy test, then you can assess whether the patient is pregnant or not based on the first day of their last menstrual period. If the individual has irregular menstrual cycles, is unsure of the first day of their last menstrual period, or is not using effective contraception, then a pregnancy test is recommended. Further, prescribers must advise individuals of child during potential to use contraception for the duration of treatment and for four days after the last dose of molnupiravir. Regarding sexually active individuals with partners with childbearing potential, they should be advised to use contraception during treatment, and for at least three months after the last dose of molnupiravir.

Prescribers must make individuals of childbearing potential aware of the pregnancy surveillance program, and we find that this is particularly in the event that a patient would become pregnant, or learn that they're pregnant while they're completing molnupiravir, or shortly after completing molnupiravir, so that they're aware of this program, and could potentially participate in the surveillance program to allow us to collect this important information. And then, I went over previously, the unique prescriber requirements pertain to use during pregnancy.

Some common questions regarding the use of molnupiravir, "How can you obtain molnupiravir for an eligible patient?" My answer is because the same is Dr. Troy's you again, need a prescription from a physician in advanced practice, registered nurse or a physician assistant who's authorized to prescribe drugs such as anti infectives. And in terms of logistically identifying where patients can access molnupiravir, I'll refer you to the COVID-19 therapeutic SPO website. The next question I have is, "Is molnupiravir active against the Omnicron variant?" There are no clinical data regarding the use of molnupiravir in patients infected with on however preliminary of in vitro data show that VIR retains its activity against the Omnicron variant. Further activity against Omicron and other variants is expected based on the mechanism of action of molnupiravir, and the fact that the drug target is conserved across different SARS-CoV-2 variants. And last, "Is molnupiravir mutagenic to patients?" This has been a highly discussed topic and based on the totality of the available data combined with the short five day treatment course, the risk of mutagenicity to patients is considered to be low. However, if this is something that you're interested in learning more about, I recommend that you look up the review documents for the molnupiravir EUA, which will provide a wealth of information on the data available

that supported this determination.

And again, here are some helpful links. This link will take you to various EUA documents, and again, you can access the patient fact sheets there, as well as the letters of authorization. Here is where you can access the scientific review documents. And again, I refer you to this. If you have further questions regarding the mutagenicity topic, or any other topics pertaining to molnupiravir. And this third bullet will take you to the COVID-19 therapeutics locator, and I've also provided an email address for questions regarding accessing various COVID-19 therapeutics. And then, lastly, the website for the NIH treatment guidelines for information on the various treatment options and the prioritization of those options, as well as definitions of disease severity. And with that, I will conclude thank you very much.

**Dr. Harmon:** Boy, that's a lot of stuff. I cannot imagine how anybody could not find this incredibly valuable. It's just the amount of information available is just in incredible. So thanks all of you, Aimee, John, Stephanie, just brilliant information. We do have a couple of questions that we have taken, and have pre prepared some of them because of the depth and the breadth of the discussion today. So, let me address a couple of the. If you don't mind, the first one that comes to mind is, do we have any timeline for better availability of any new antivirals and are additional monoclonal antibodies? I know we've got some of the current product [inaudible 00:39:39], but it's really a little bit in some of us, it's just short supply. Maybe some additional monoclonal antibodies, do you see have any timeline for that, or any new antivirals? Anybody?

**Dr. Farley:** Sure. So this is John. I can start with a few remarks. So, I think, for all of us as health care providers, and particularly for those of you on the front line, this has been a very difficult winter and it's not over yet. I think for Paxlovid in particular, the US government and the company are working as hard as they can to improve the supply of that product, and I would expect the at that should improve considerably come the spring. So in a relatively short period of time, but we have a period of continued short supply ahead.

I think the issues with sotrovimab really illustrate the Achilles heel of the monoclonal antibodies, because they are dependent upon binding to the spike protein of the virus to work and with all of the variants, one of the key characteristics of the variants is changes in the spike protein. So monitoring this situation is complex. It's a partnership between the FDA, and the CDC, and a number of branches of government. But, I think it's unfortunate that we really have for now, lost two of the antibodies that we were really very dependent upon because they simply are not expected to be a benefit to the patient. We're working hard to improve the supply of sotrovimab, and I think at will improve over time as well.

I think that the Remdesivir addition to the outpatient armamentarium is important. It's a drug that many, many providers are familiar with from the last year and a half or two years. Right now, the distribution pattern has been to hospitals because it was for hospitalized patients, but I know that

Gilead is working to expand its distribution plan, so that we can begin to bring in more and more outpatient facilities to have access to that drug. So I'll stop there on that question.

**Dr. Harmon:** Thanks Dr. Farley, anybody want to add anything? If not, I've got plenty of questions and I really appreciate the answers, thanks all. I heard a good conversation, I was watching all the presentations and there's some commentaries I'd like to ask; can you be a little more specific and maybe reiterate the treatment options for are and teens because I'm seeing more and more in my first line population of my children, and those under 18 who are sick, and so I want to be sure that I have this straight about the treatment options for them. Can anybody comment with a little more depth on the treatment options for children and teens?

**Dr. Troy:** I can start, and then I can pass off to Dr. Farley. I'll just mention that Paxlovid again, is authorized for teenagers, for adolescents who are at high risk for progression to severe COVID. And I believe sotrovimab is also authorized for adolescents. And Remdesivir is authorized down to 3.5 kilograms, so those three right now, are our treatment options for kids and adolescents.

**Dr. Hodowanec:** And I'll just reiterate again, that molnupiravir is not authorized for anyone less than 18 years of age, that would not be an option for any pediatric population.

**Dr. Farley:** Yeah, just a closing comment on that; we're working with companies to accrue pediatric data, but I'm a pediatrician myself, and from what my colleagues make very clear to me is what they want to see is pediatric pharmacokinetic data, as well as some safety data in children before they feel comfortable. So we're trying to provide that. We certainly have that with Remdesivir right now, and we're working with the other companies to try and accrue that information for the pediatric community.

**Dr. Harmon:** Thanks. I really appreciate that clarification. This is going to be, it's a common thing that I come across as a frontline clinician and some of my colleagues will say that, "Herman you're on the front lines, you're AMA, tell me, is there a difference between molnupiravir and sotrovimab in a specific patient population given equal access to both?" And so, I don't know, you're the clinicians and they're recommending scientists; would you consider molnupiravir versus sotrovimab and a patient in a specific patient population if just equally available?

**Dr. Hodowanec:** Sure. So, I'll start, as I mentioned in my presentation, molnupiravir is only authorized for use in patients for whom alternative COVID-19 treatment options are not accessible or clinically appropriate. So if both sotrovimab and molnupiravir were available, unless there was some other reason that sotrovimab was considered not clinically appropriate for a given patient; maybe a history of hypersensitivity, if they'd previously been exposed, something like that, otherwise generally, sotrovimab would be used over molnupiravir. But in general, I would refer you and other physicians to the NIH treatment guidelines, which have information on all of the available options for the treatment of outpatients, with mild to moderate COVID-19, and the various considerations for different patient characteristics and such, that might make you choose one over another, based on availability as well.

**Dr. Harmon:** Thanks, Aimee. I appreciate that. And here's an interesting thought, and I was looking at this pre-submitted question; there are timeframes in which antivirals or prescription treatments must be initiated in order to be effective, but I get this phone call a lot from some of my patients that, is there a benefit to people who might have initially mild disease, but then worsen? I guess you want to start it as soon as you can, but suppose they start off and say, "I'm not that high risk. I feel pretty well." In two or three days into the illness, they say, "I'm pretty sick. Dr. Harmon, I'm starting to get cough, fever," is there a benefit or unlikely benefit from starting even then? Do you have a thought process of that?

**Dr. Troy:** I can start with Paxlovid, and just to say that we actually don't have any data with anyone who was dosed past five days from symptom onset. So, they did compare people who received it up to three days, and people received it four to five days after symptom onset, and there wasn't a difference. So it seemed to have the same treatment effect in both those populations, but we don't have any data for beyond five days from symptom onset. And the earlier the better, like you mentioned.

**Dr. Hodowanec:** Similarly from molnupiravir, it was studied in patients who are within five days of symptom onset. And that is how it's authorized to be used. And further, it's authorized for patients with mild to moderate illness. That said if a patient were to start molnupiravir with mild to moderate illness and progress while they were receiving molnupiravir, they would be able to complete their five day treatment course for their provider's discretion. But there aren't data or recommendation to, to start in patients who have already progressed beyond that mild to moderate disease severity.

**Dr. Farley:** Just to round it out with, with remdesivir; we have two more days because that trial, I think, was up to seven days of symptom onset. And the FDA generally, as most of you know, in it's labeling and recommendations tends to stick pretty close to the data in terms of what the clinical trials demonstrated. So, that's what we're able to present to the medical community at this time. And particularly for an authorization of an unapproved drug, which is really what an EUA is. We tend to be pretty strict about that in terms of what we're able to advise.

**Dr. Harmon:** And John and all thank you. I know what the answer to this question's going to be, but it was submitted, and I thought it was reasonable, because we still deal with it every day as a front line provider dealing with folks, let's say they're in the ICU. They're COVID positive patients. They're in the ICU, they're ventilated, we're telling the family we're expecting that this patient will not survive. And the family and some of my clinicians will say, is there either medicine, the Paxlovid or molnupiravir affective when started that the patients are already intubated and likely to die? I know this outside the EUA, and so my answer has been, "They're outside the EUA, it's not likely to help," but hearing this group talk about that may be worthwhile for this audience.

**Dr. Troy:** I can start again for Paxlovid, and firstly, we don't have any data in hospitalized patients. So, it's really unknown whether it helped them. The good news is that I think I mentioned during my talk that in the patients who had the positive antibodies at baseline, there was still a positive treatment

effect. So that I think is a positive sign, but we really don't have any data for use in hospitalized patients, particularly ones who are intubated.

**Dr. Hodowanec:** And I can comment on molnupiravir. Molnupiravir there are some data from hospitalized patients that have been published that did not show a treatment benefit associated with molnupiravir and hospitalized patients. And notably, those were hospital patients who were not considered to be critically ill. So they were not patients who were intubated, or met other critical disease severity criteria at the time of enrollment. And again, those data have been published if viewers would like to learn more about that data.

**Dr. Farley:** Yeah. And of course, remdesivir is approved through the continuum of the disease. It's one of the few drugs that is. So we do have an approval for hospitalized patients and has been commonly used. I think, the case that you're citing, of course, we're fairly far along into the inflammatory aspects of the disease. And there are also a range of therapeutics approved specifically to address the inflammatory component of the disease, which physicians should consider. And those are really well detailed in the NIH treatment guidelines, as well as the IDSA treatment guidelines.

**Dr. Harmon:** Thanks all. And we got a few minutes and I've got time for one more question I'm going to submit, and this is kind of an off the wall question, but I thought it, when I read it. Let's say you have Paxlovid or molnupiravir available, and you have patients who self-diagnose using a home test, and they're traveling internationally. I mean, all these things are unfortunate, they're no longer theoretical; they're real. People will be traveling internationally. They'll be outside the US, and they'll self-diagnose, they have a home test kit. "Whoops, I've got COVID and I'm in Paris, or I'm wherever happened to be." Is there any Paxlovid, or something be suitable if they could obtain for patients who self-diagnose using that home test while traveling?

**Dr. Hodowanec:** I can go first, I guess in general, I believe both Paxlovid and the molnupiravir EUA do not specify how the diagnosis of COVID-19 must be made, whether it's as an antigen test or a PCR, whether it's a home test versus in an office test. So, it's up to a prescriber's discretion to take the data that they have available as to whether or not the patient has SARS-CoV-2 infection. So potentially, yes, it could be used in a patient who tests positive with a home management test, here or abroad.

**Dr. Harmon:** One more question, then we'll end. I didn't hear a lot now, but I'm still called by patients and other clinicians, is there much use for steroid use in the ambulatory positive test patient right now? They're not used as often. I tend to not use them as often in my personal treatment plans for patients, but is there still a place for steroid use in the outpatient treatment at this point?

**Dr. Farley:** Sure. So from what I know, there is not evidence of benefit at that early point in the disease for the use of steroids. It's certainly a question for which there's equipoise, and there are trials underway to try and address that question. But to my knowledge, we don't have any evidence that

would be actionable at this point.

**Dr. Harmon:** Well, thanks everybody. I know we've had a busy time today. I've learned a lot, I hope everybody else has. You all have been more than gracious with your time, colleagues, and it's just exciting to be a part of it. Thank you. Thank you so much. I'd like to thank you for your time, your commitment to identifying the best ways that we can respond to of the COVID pandemic. Thank you, Dr. Troy, Hodowanec and Farley for updating us, and helping us so much. I took a lot away and I thank you very much.

I'd like all in the audience to know that at AMA, we're continuing these webinars. Today's our tenth webinar on COVID, the challenges we're facing, the opportunities we have and how we're responding to it. Our previous sessions have covered a wide range of topics, including pediatric vaccines and boosters, the FDA vaccine review process, the vaccine development, vaccine safety and development delivery and confronting vaccine misinformation. If you weren't able to join us for these, they're accessible on our website. The link, hopefully, we'll share it in the chat here in a moment. You can simply visit our AMA web page and search for COVID-19 webinar, that's [www.ama-assn.org](http://www.ama-assn.org). We have additional webinars in the works, we'll keep you apprised of the future dates, the topics and events. Any closing comments from you, John, Stephanie, or Aimee for our audience here.

**Dr. Farley:** Yeah, no, I just want to thank the audience because I know that that they are on the front lines every day, working to take care of patients, and we at FDA are work to provide you with the best information we can for treatment options. So thank you very much for all that you do every day.

**Dr. Harmon:** Echo Dr. Farley; it's really a privilege to be where we are in medicine today. This is where we're all trained for; for epidemics like this. We would hope we never have to exercise those training and skills in a pandemic, but I appreciate all my physician colleagues, all of us at every level. Researchers, frontline workers, you're all my heroes and heroines. Thank you very much. You all have a good day. Until next time, be safe. Thank you.

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