Nine things you need to know about the new COVID-19 pill

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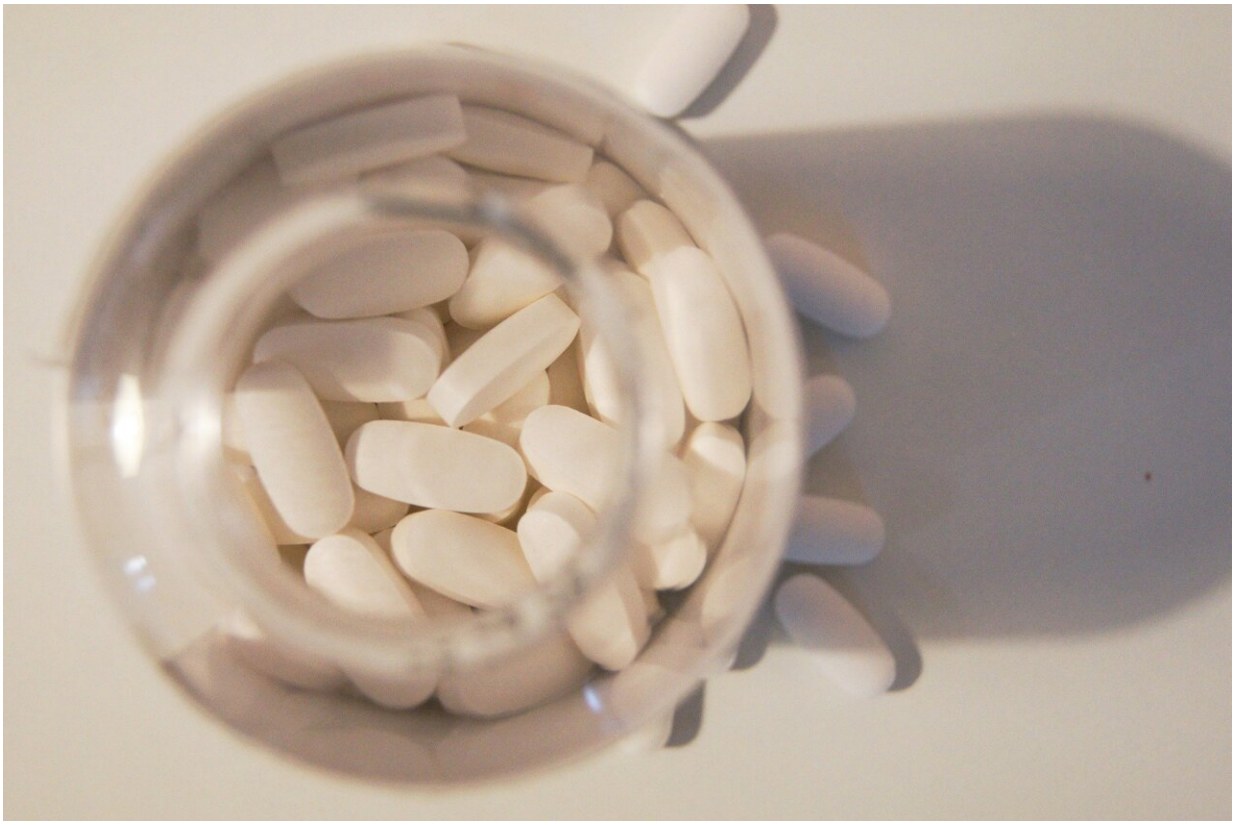

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Over the past year, discussions—sometimes heated ones—about ending the COVID-19 pandemic have largely focused on the availability, effectiveness, and safety of vaccines. But in early October, Merck

reported on a promising new drug treatment that could be given as a pill in the days after COVID-19 symptoms arise to prevent severe disease. This news, which many are hailing as a potential game-changer, is already starting to change the conversation.

Merck has applied to the Food and Drug Administration (FDA) for emergency use authorization (EUA) of the pill, called molnupiravir. While an authorization could become available in a matter of weeks, it's not yet clear who would get it. But what we do know is that the company says it performed so well in a clinical trial that it halted the trial early, so it could move quickly to apply for the EUA. A company press release reports that the drug cut the risk of hospitalization and death by half in patients who had mild-to-moderate disease.

"It certainly has the potential to be a really important advance," says Albert Shaw, MD, Ph.D., a Yale Medicine infectious diseases specialist. "Other COVID-19 treatments, such as remdesivir or monoclonal antibodies against the SARS-CoV-2 virus causing COVID-19, are given intravenously. This is a pill your physician could write a prescription for, that you could pick up in a drugstore."

We asked Dr. Shaw and other infectious disease experts to answer commonly asked questions about Merck's new COVID pill.

1. How does the COVID-19 pill (molnupiravir) work?

It's important to note that the pill is meant to be taken after you've experienced COVID-19 symptoms. In the clinical trial, molnupiravir was given to study participants in four capsules twice a day for five days—starting within five days after patients experienced the first symptoms of COVID-19.

When the drug enters your bloodstream, it blocks the ability of the

SARS-CoV-2 virus to replicate, Dr. Shaw explains.

The coronavirus uses RNA as its genetic material. The structure of molnupiravir resembles the nucleosides (or chemical building blocks) used to make the virus's RNA. The drug works by incorporating itself into the RNA as it's being synthesized.

"This results in many mutations, or changes in the RNA genetic code, introduced into the viral RNA," says Dr. Shaw. "And when this RNA is translated into viral proteins, these proteins contain too many mutations for the virus to function."

2. Does molnupiravir have any side effects?

Based on the data in the company's release, the drug appears to have a clean safety profile, meaning there were no serious side effects in trial volunteers.

Because molnupiravir works by disrupting how the coronavirus replicates RNA, there could be a concern of a similar effect on human DNA or RNA. Merck reportedly has data from laboratory studies indicating that molnupiravir does not cause mutations in humans, but "the FDA will obviously need to see and evaluate this safety data in the approval process," Dr. Shaw says.

Dr. Shaw notes that several approved antiviral drugs already in wide clinical use—such as acyclovir and related drugs for herpesvirus infections, and reverse-transcriptase inhibitors for HIV infection—also work (via different mechanisms) in interfering with the replication of viral DNA or RNA.

Yale Medicine infectious diseases specialist Jaimie Meyer, MD, MS, noted that in its clinical trial, Merck didn't test the drug on pregnant

women. "In the trial, not only did they exclude women who were pregnant, breastfeeding, or anticipating becoming pregnant, but they also told the men enrolled in the trial that they couldn't have unprotected sex with women for a week after they were done with their medication," she says.

The concern might be that this drug would interfere with RNA replication needed for fetus development and cause birth defects. This will be important to tease out as this drug moves from clinical trials to the market, she adds.

3. Is molnupiravir similar to Tamiflu?

Yes, this new pill is similar—in function, ease of use, and availability—to Tamiflu, the antiviral medication that is used to prevent serious symptoms of flu. There is a key difference, though, says Dr. Shaw. "Tamiflu works through a different mechanism—by interfering with the entry of influenza virus into cells—instead of targeting the reproduction of viral RNA," he says.

Interestingly, Tamiflu also can be given in a single dose to prevent infection with the flu, "like a post-exposure prophylaxis [PEP]," says Dr. Meyer, explaining how some people may be prescribed antiviral medications after a potential exposure to a disease, like HIV, to prevent infection. "Molnupiravir has not yet been tested as a PEP against COVID-19," she says, "but that would be a hope for the future."

4. Does molnupiravir prevent infection or severe illness and death?

The goal of the Merck pill is to keep people out of the hospital, explains Dr. Meyer. "We want to prevent severe illness and death in people who

are infected with mild-to-moderate COVID, but who are not yet hospitalized," says Dr. Meyer. The Merck study suggested that molnupiravir would help patients who have at least one risk factor for severe COVID-19 to avoid hospitalization.

5. Who is molnupiravir recommended for?

Merck is seeking an EUA for its pill for high-risk adults. In the clinical trial, molnupiravir was mostly given to people who were over 60 or those who were younger but had other conditions that put them at high risk of bad outcomes from COVID-19, such as diabetes, heart disease, or obesity. The FDA will also decide whether it should be given to vaccinated people—only unvaccinated individuals were included in the trial.

6. Will molnupiravir work on virus variants, including Delta?

Yes, in what may come as a relief to many. The research, which was conducted in the U.S. and other countries, also suggests the drug would be effective against mutations of the virus that the Centers for Disease Control & Prevention (CDC) classifies as "variants of concern," including the Delta, Gamma, and Mu mutations.

7. Could molnupiravir be a turning point for other COVID-19 treatments?

So far, treatments for COVID-19 have been hard to deliver or not very effective. "We don't have a lot of COVID medications in our arsenal," Dr. Shaw says. Remdesivir, the only COVID-19 drug treatment fully approved by the FDA, can only be administered intravenously in the hospital. It's also only for those ages 12 and older, regardless of how

severe their symptoms are, and studies suggest it may provide only modest benefit.

But there are other drugs in the pipeline for the treatment of COVID-19, says Dr. Shaw. Pfizer, which produced the first COVID-19 vaccine to be authorized—and later fully approved—in the U.S., is expected to report results on a promising protease inhibitor that would also be given in pill form. "Hopefully, there will be more tools to help us better treat our COVID patients," he says.

8. Why was the trial stopped early?

The trial was halted on the recommendation of a data and safety monitoring board, an independent committee charged with evaluating progress of the study at specified intervals.

"This is not uncommon in clinical trials," Dr. Shaw says. "In consultations with statisticians, and without input from Merck, the board concluded that the results showing efficacy were clear and would not be affected by continuation of the trial—and, that the best thing would be to stop the trial and make the results known, so we can move forward."

It's important to note that at the time the study was stopped, they were 70% fully enrolled, "so they had data on nearly 800 individuals randomized to receive either the study drug or the placebo," adds Dr. Meyer.

9. If molnupiravir is authorized, do we still need vaccines?

Both doctors emphasized that if and when molnupiravir is authorized—and even if it is as successful in real-world scenarios as it

was in the study—vaccination will remain essential for preventing SARS-CoV-2 infection—and for slowing its spread. People who are vaccinated have a much lower chance of getting sick and needing any treatment, they say.

"The vaccine is our first-line tool for preventing hospitalization, and I'm a little concerned that the attention on molnupiravir will draw attention away from vaccination," says Dr. Meyer. "Some people might say, "I'm not getting vaccinated because I'll have access to these medications'—to this pill or to remdesivir or other treatments. But you can't trade one for the other. If you haven't done so already, the most important thing is still to get the vaccine."

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