FDA OKs Second COVID Antiviral Pill for Limited Use

Molnupiravir is authorized for people at high risk for severe COVID-19 when other treatment options are not available.

December 23, 2021 By Liz Highleyman

On December 23, the Food and Drug Administration (FDA) granted emergency use authorization of molnupiravir as the second antiviral pill for the treatment of COVID-19. The agency limited its use to adults at high risk for progression to severe disease for whom alternative authorized treatment options are not accessible or appropriate.

The move comes on the heels of the approval of Pfizer's Paxlovid (nirmatrelvir plus ritonavir). While molnupiravir, from Merck and Ridgeback Biotherapeutics, is less effective than Paxlovid and has some significant safety issues, it may initially be more widely available.

"Today's authorization provides an additional treatment option against the COVID-19 virus in the form of a pill that can be taken orally. Molnupiravir is limited to situations where other FDA-authorized treatments for COVID-19 are inaccessible or are not clinically appropriate and will be a useful treatment option for some patients with COVID-19 at high risk of hospitalization or death," Patrizia Cavazzoni, MD, director of the FDA's Center for Drug Evaluation and Research, said in a news release. "As new variants of the virus continue to emerge, it is crucial to expand the country's arsenal of COVID-19 therapies using emergency use authorization, while continuing to generate additional data on their safety and effectiveness."

FDA issued an EUA for molnupiravir for the treatment of mild-to-moderate #COVID19 in adults with positive results of direct SARS-CoV-2 viral testing. https://t.co/ZTuuN6oJ4b pic.twitter.com/n2InjtWSfd

— U.S. FDA (@US_FDA) December 23, 2021

Molnupiravir is authorized for adults ages 18 and older, while Paxlovid is authorized for those ages 12 and up. Both pills are indicated for people who test positive for SARS-CoV-2 (the coronavirus that causes COVID-19), have recent mild to moderate symptoms and are at high risk for progression to severe disease. Both are available by prescription only and must be started within five days of symptom onset. Molnupiravir is administered as four capsules taken every 12 hours for five days.

Neither pill is intended for people who are at risk for exposure to SARS-CoV-2 (pre-exposure prophylaxis), those who have recently been exposed to someone with the virus (post-exposure prophylaxis) or those who already require hospitalization for severe COVID-19. And they should not be considered a substitute for vaccination.

Despite the rapid availability of highly effective COVID-19 vaccines, effective oral antiviral treatment for early disease has taken longer to develop. Monoclonal antibodies are used to prevent disease progression, but they require injection or IV infusion. Other medications, including remdesivir (Veklury) and dexamethasone, are used to treat hospitalized patients with more severe disease.

Molnupiravir (formerly known as EIDD-2801 or MK-4482; sold under the brand name Lagevrio in Europe) is a nucleoside analogue, in the same broad class as some medications used to treat HIV and hepatitis B and C. However, it works differently, causing the accumulation of so many mutations in the SARS-CoV-2 genetic code that the virus is no longer able to replicate. Early research showed that molnupiravir stopped SARS-CoV-2 replication in human lung cells in the laboratory and reduced viral load in hamsters.

Molnupiravir Safety and Effectiveness

The FDA authorization was based on results from the Phase III MOVe-OUT trial (NCT04575597), which included 775 unvaccinated, nonhospitalized adults who tested positive for SARS-CoV-2, had mild to moderate COVID-19 symptoms for no more than five days and had least one risk factor for poor disease outcomes, such as older age or underlying health conditions. They were randomly assigned to receive molnupiravir or placebo pills for five days.

In early October, Merck announced results from a planned interim analysis showing that 7.3% of molnupiravir recipients were hospitalized or died within a month, compared with 14.1% of placebo recipients—a nearly 50% risk reduction. However, further analysis of a larger group of 1,433 participants showed that 6.8% of molnupiravir recipients versus 9.7% of placebo recipients were hospitalized or died, falling to a 30% risk reduction. Although the effectiveness was substantially lower than previously reported, there was just one death in the molnupiravir group compared with nine in the placebo group. In comparison, Paxlovid reduces the risk of hospitalization of death by about 90%. Early laboratory data suggest that molnupiravir works against the Omicron variant, which has many mutations in its spike protein that compromise the effectiveness of vaccines and most monoclonal antibodies.

Treatment was well tolerated and adverse effects were comparable in the molnupiravir and

placebo groups; few people discontinued treatment for this reason. The most common adverse events are diarrhea, nausea and dizziness, mostly mild or moderate.

Unlike Paxlovid, molnupiravir does not need to be administered with ritonavir, a boosting agent that slows drug metabolism and is contraindicated with many other medications due to drug interactions. No drug interactions have been identified for molnupiravir. In addition, molnupiravir does not carry the same warnings to use with caution in people with liver or kidney disease.

However, some experts are concerned that molnupiravir could potentially cause genetic mutations in human DNA, although animal studies did not raise red flags. Another potential issue is that, by causing many viral mutations, the drug could promote the emergence of new variants.

Molnupiravir can potentially harm a developing fetus, and it is not recommended for use during pregnancy unless the benefits of treatment outweigh the risks for an individual patient. Women and men of reproductive potential should use reliable contraception while taking molnupiravir and for four days (for women) or three months (for men) after the last dose. Molnupiravir is not authorized for people under 18 because it may affect bone and cartilage growth.

Given molnupiravir's modest effectiveness and safety concerns, the FDA's Antimicrobial Drugs Advisory Committee voted to recommend emergency use authorization by a narrow 13 to 10 margin.

Availability and Unanswered Questions

Merck said in a press release that it expects to begin shipping molnupiravir within days. The company said hundreds of thousands of courses are ready to ship in the U.S., with another million coming in the next few weeks, as well as several million more for worldwide distribution, STAT reported. Merck previously reached an agreement with the federal government to supply 3.1 million courses of the drug at about $700 each. The company expects to produce 10 million courses by the end of 2021 and another 20 million in 2022. Pfizer, in comparison, expects to produce just 180,000 courses of Paxlovid this year. This means molnupiravir will initially be more widely available—an important consideration as the Omicron COVID-19 variant is surging across the country.

Merck said it would offer worldwide access to molnupiravir through a tiered pricing approach based on the income level of each country. It will also grant voluntary licenses to other manufacturers and to the Medicines Patent Pool to make generic molnupiravir available in more than 100 low- and middle-income countries.

The authorization of molnupiravir and Paxlovid raises questions about the appropriate use of oral antivirals. Should they be available for everyone with early COVID-19 or only those at high risk for severe disease? How well do they work for vaccinated individuals with breakthrough infections? Could they potentially be used for COVID-19 PrEP for immunocompromised people who don't respond well to the vaccines? And in practical terms, will people be able to get tested for SARS-CoV-2 soon enough to fall within the five-day window after developing symptoms?

While issues of supply and access remain, having more treatment and prevention options on the table can help curb the pandemic. Although molnupiravir is less effective than Paxlovid at preventing hospitalization, it substantially decreased mortality. Molnupiravir may be a good option for people with liver or kidney disease and those taking drugs that interact with ritonavir, while Paxlovid is preferred for pregnant women and teens between the ages of 12 and 18.

Click here to read the prescribing information for molnupiravir.

Click here for more news about COVID-19 treatment.
