The FDA grants emergency use authorization to Pfizer and Merck's anti-COVID pills

Benjamin Mateus
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Just before the Christmas holiday, with Omicron's dominance confirmed, the Food and Drug Administration (FDA) gave emergency use authorization (EUA) to two new oral antiviral medications, Pfizer's Paxlovid and Merck's Molnupiravir. These are intended to treat people with mild to moderate COVID-19 disease confirmed by SARS-CoV-2 testing and who are considered high-risk for progression to severe illness, including hospitalization and death. The Centers for Disease Control and Prevention (CDC) are expected to endorse these recommendations soon.

First, on December 22, the FDA announced Pfizer's Paxlovid, a two-drug regimen consisting of two tablets of Nirmatrelvir and one tablet of Ritonavir, taken twice daily for five consecutive days (30 tablets in total). The treatment would be available to patients 12 years and up, by prescription only, after the diagnosis of COVID-19 and within five days from the onset of symptoms.

Primary data supporting the FDA EUA comes from the EPIC-HR [**E**valuation of **P**rotease **I**nhibition for **C** OVID-19 in **H**igh-**R**isk Patients] trial that enrolled participants 18 years and older, but was extended to include high-risk pediatric patients. The active ingredient Nirmatrelvir is a protease inhibitor that stops the virus from replicating. The second drug Ritonavir helps slow the metabolism of Nirmatrelvir, allowing it to remain in the body at higher concentrations.

Then, on December 23, the FDA granted Merck's Molnupiravir an EUA with similar parameters for initiating treatment—within five days of symptoms and confirmation of infection with viral testing. A prescription from a medical provider is also required. However, the medication is only authorized for those 18 or up due to the drug's potential impact on bone and cartilage growth. Like Paxlovid, the treatment has not received approval for use before exposure to SARS-CoV-2, the virus that causes COVID-19, or for patients after exposure if they have not tested positive. The regimen for Molnupiravir requires four tablets taken twice daily for five consecutive days (40 pills total).

The two oral antiviral treatments against COVID-19 have different mechanisms of action.

Molnupiravir works by introducing errors into the SARS-CoV-2's genetic code. The active ingredient, a molecule called N4-Hydroxyctyidine (NHC), once it has been incorporated into the virus's RNA, can undergo a chemical reaction called tautomerization, allowing it to rapidly flip back and forth between two nucleotides, Cytidine and Uracil. When the virus attempts to replicate again, multiple errors are incorporated because of the change in forms of NHC during RNA strand replication, leading to a lethal mutation that leaves the virus unable to infect or reproduce.

Pfizer's medicinal chemists designed their drug against the virus's main protease enzyme known as *Mpro* or *3CLpro*, with the caveat that it be given orally. After the virus creates a long polyprotein chain, the protease enzyme cleaves the chain into functional proteins used to assemble itself and multiply. Speaking with *Chemical and Engineering News* in March 2020 , Professor Matthew Todd, chair of drug discovery at University College London, said, "The protease is essential [for the virus], but has no human homologs [a gene related to a second gene by descent from a common ancestral DNA sequence]."

The implication is that viral protease inhibitors would have little chance of affecting human protease enzymes. Additionally, the protease of the Omicron variant is similar to the protease of the ancestral strain, meaning current mutations of SARS-CoV-2 remain susceptible to this line of treatment.

After initiating a phase one trial in late March 2021 on healthy adults to assess safety and tolerability profiles for their new drug, Pfizer unveiled their oral SARS-CoV-2

inhibitor to the public in April 2021 at the American Chemical Society's spring meeting. By the end of July, the Pfizer pill had demonstrated both tolerability and more than adequate concentration levels needed to inhibit SARS-CoV-2 replication. This prompted a phase 2/3 clinical trial with the plan to enroll 3,000 participants in a randomized double-blinded study.

On September 1, Pfizer told regulators that the first participant in their trial had been enrolled. They also indicated they were adding a low dose of Ritonavir to the treatment regimen. Ritonavir is an antiretroviral medication used to treat HIV/AIDS. It helps slow the metabolism of Nirmatrelvir, allowing it to remain at higher concentrations in the body for a more extended period.

Then, more than a month after Merck's interim findings demonstrated a 50 percent reduction in risk of hospitalization and death among COVID-19 positive high-risk patients treated with Molnupiravir, Pfizer announced on November 5 an interim analysis showing a remarkable 89 percent reduction in hospitalization and death as compared to those taking the placebo pills. Only three out of 389 participants (0.8 percent) taking Paxlovid were hospitalized, and no deaths occurred among those receiving the investigational drug. By comparison, in those receiving a placebo, 27 out of 385 participants (7.0 percent) were hospitalized, with seven subsequent deaths.

At the recommendation of the independent Data Monitoring Committee and in consultation with the US FDA, further enrollment into the study was discontinued so that the drug could be put into general use more rapidly. Based on the overwhelming efficacy of the data, Pfizer requested emergency use authorization from the FDA.

Subsequently, at the end of November, Merck announced the discouraging results of their final analysis from their final trial. They had to revise downward to 30 percent their estimates on Molnupiravir's ability to prevent hospitalization among high-risk COVID patients (68 out of 699 (9.7 percent) in the placebo group versus 48 out of 709 (6.8 percent) in those receiving Molnupiravir). On a brighter note, they highlighted that while there were nine deaths among the placebo group, only one participant died taking the investigational drug, suggesting it is highly beneficial in preventing deaths.

By contrast, Pfizer's recent final analysis results remained unchanged, suggesting that Paxlovid can prevent far more hospitalizations than Merck's Molnupiravir. The two drugs appear to have similar efficacy in preventing deaths, though the numbers were too small to offer a cross-study comparison. In the last Pfizer study, 12 people died in the placebo group while no one died taking Paxlovid.

However, concerns have been raised that the use of Paxlovid in people with uncontrolled or undiagnosed HIV-1 infections could lead to possible HIV-1 drug resistance. Those with pre-existing liver or kidney disease or who use medications that could interact with Paxlovid should consult their physician to ensure the treatment is suitable.

According to CNN last month, on news of positive results for Paxlovid, the Biden administration announced it would purchase 10 million treatment courses for $5.3 billion. This is on top of 3.1 million treatment courses for Merck's Molnupiravir, at a cost of $2.2 billion. Biden promised that more than 250,000 courses of Paxlovid would be available in January, and both giant pharmaceuticals are intending to ramp up production to meet continued demands for the treatment of symptomatic COVID-19.

With $36 billion in worldwide sales of its COVID-19 vaccines this year and a projected $18 billion in sales for Paxlovid next year, Pfizer is in a position to enrich their investors with obscene sums of money. The spread of Omicron and the White House opposition to any form of lockdown or other significant public health effort have assured Wall Street that pandemic profiteering will continue unabated. The White House has guaranteed it will not lift a finger to prevent the spread of infection, while SARS-CoV-2 enjoys a wide berth in finding new ways to mutate continuously.

The development of these treatments is without doubt a testament to the scientific ingenuity and collaborative effort that have made possible designing, testing and producing these drugs in a few short months. However, they also underscore the criminal negligence and failures of governments to implement broad public health measures that could have ended the pandemic once and for all, instead of ensuring dependence on such treatments to save just a fraction of lives that could have been saved through an elimination strategy.