Covid-19: What is the evidence for the antiviral Paxlovid?

With clinical evidence behind it growing, the combination treatment is moving from the laboratory to patients around the world at record speed, reports Andy Extance

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What is it?

Paxlovid is an antiviral combination developed by the pharmaceutical giant Pfizer. The treatment includes the newly developed antiviral drug nirmatrelvir and ritonavir, a potent inhibitor of the cytochrome P450-3A4 (CYP3A4) enzyme that metabolises several classes of drugs. Ritonavir slows down nirmatrelvir’s breakdown, thereby increasing drug concentrations and delaying clearance.

Patients take Paxlovid as three tablets, two 150 mg tablets of nirmatrelvir and one 100 mg tablet of ritonavir together, twice daily for five days. As with the covid antiviral treatment molnupiravir,1 the oral route of delivery makes it convenient to take at home, unlike some other drugs for covid-19, which require intravenous infusion.

Who is eligible for treatment?

It is authorised for people older than 12 years old, weighing more than 40 kg, who have mild to moderate covid-19, and who are at high risk of progression to severe symptoms, hospital admission, or death. Treatment should start as soon as possible after diagnosis and within five days of the onset of symptoms. On 9 March this year Pfizer started a phase 2/3 trial in 140 children aged 18 or younger.2

How does Paxlovid work?

When SARS-CoV-2 RNA enters an infected cell, it uses its host’s translational machinery to make the proteins needed for the virus to function and assemble new copies of itself. That machinery translates the virus genome into two large polyproteins, which two protease enzymes then cut up into smaller pieces.3 One of them is SARS-CoV-2’s main polyprotein protease enzyme, SARS-CoV-2 Mpro. Nirmatrelvir blocks SARS-CoV-2 Mpro, so that it can’t bind the polyprotein. That leaves the virus unable to make any functional proteins and therefore unable to replicate. SARS-CoV-2 Mpro is unlike any human protease, which should limit the drug’s toxicity.

Nirmatrelvir originated from a Pfizer research programme into the original SARS in 2002. That led to an intravenous preclinical candidate, PF-00825221, which worked well against SARS-CoV-2. Starting in February 2020, Pfizer sought to adapt this into a drug that could work orally. In one week in July 2020 its scientists prepared 20 drug candidates, of which nirmatrelvir was one.4

Ritonavir is also a protease inhibitor originally developed to treat HIV-1 infections. In Paxlovid, it inhibits nirmatrelvir breakdown in the liver so that nirmatrelvir reaches higher drug concentrations and is eliminated more slowly. The effect of ritonavir on P450 can be a problem if patients are taking other drugs that this enzyme breaks down. These include anticoagulants, anticonvulsants, corticosteroids, pethidine, amiodarone, flecainide, colchicine, ciclosporin, lovastatin, simvastatin, sildenafil, and midazolam.

What peer reviewed evidence is there for Paxlovid?

While nirmatrelvir was designed specifically to target SARS-CoV-2 Mpro, in vitro analysis showed it stopped SARS-CoV-1, SARS-CoV-2, MERS, and 229e coronaviruses affecting cells.5 It also protected mice against SARS-CoV-2 when taken orally. By the time those results were published, Pfizer had already completed a phase 1 clinical trial in healthy participants and started a phase 2/3 trial, called EPIC-HR, for covid-19.5 6 The phase 1 trial studied nirmatrelvir as a single agent and also in combination with ritonavir. Finding that drug concentrations remained higher for longer in the combination, Pfizer used it in EPIC-HR, which randomised 2246 patients, with 1120 receiving 300 mg of nirmatrelvir and 100 mg of ritonavir and 1126 receiving placebo twice daily for five days.

On 5 November 2021 Pfizer announced an interim analysis of 774 patients who were treated within three days of symptom onset.7 Just three of 389 patients (0.77%) who received Paxlovid had been admitted to hospital by day 28. Twenty of 385 patients taking placebo had been admitted in this time, and a further seven had died; those 27 people comprising 7% of the placebo group.

Pfizer announced the final data on 14 December, publishing them in the New England Journal of Medicine on 16 February.8 The primary analysis again looked at patients who had received Paxlovid within three days of symptom onset. Five of 697 patients (0.72%) receiving Paxlovid had been admitted to hospital by day 28. In the placebo group, 35 of 682 patients had been admitted in this time, and a further nine had died, those 44 people comprising 6.45% of the placebo group. When the analysis was extended to people who received Paxlovid within five days of symptom onset, the data showed that eight of 1039 patients (0.77%) in the Paxlovid group and 66 of 1046 (6.31%) in the placebo group had been admitted to hospital with covid-19 or died from any cause through to day 28. The consistency between the interim and
Although three are not yet peer reviewed, in January 2022 Pfizer published four BioRxiv preprints regarding effectiveness of Paxlovid against the covid-19 variants of concern, including omicron. One preprint showed that Paxlovid retained its efficacy against variants and another showed why. Two further studies also showed that Paxlovid, remdesivir, and molnupiravir all retained their activity against such variants, one of which has now been peer reviewed and published in Antiviral Research.

Which countries are using Paxlovid?

Pfizer sought emergency use authorisation for Paxlovid from the US Food and Drug Administration 11 days after press releasing its interim analysis, on 16 November 2021. It received that authorisation on 22 December, less than a year after the first patient received the drug in clinical trials and only two years after the pandemic began. Scientists have hailed this as the fastest drug development project on record.

Israel’s health ministry approved Paxlovid on 26 December 2021, as did the UK’s Medicines and Healthcare Products Regulatory Agency on 31 December. The European Medicines Agency recommended conditional marketing authorisation on 27 January 2022. And on 11 February China’s National Medical Products Administration granted Paxlovid emergency approval, the first foreign drug or vaccine the country had approved for covid-19.

On 17 March the United Nations backed Medicines Patent Pool signed agreements with 35 manufacturers of generic drugs in Europe, Asia, and Central and South America to make Paxlovid and supply it to 95 poorer countries. Then, on 22 March Pfizer agreed with Unicef to supply four million courses of treatment to 95 low and middle income countries, pending authorisation or approval, beginning in April 2022. Two days later, the Africa Centres for Disease Control and Prevention agreed to a memorandum of understanding with Pfizer to provide Paxlovid for African countries. However, availability in India of a locally made generic version of Paxlovid has been held up by a requirement of the country’s Central Drugs Standard Control Organisation for extra trials.

At the time of writing, the World Health Organization’s assessment of nirmatrelvir and ritonavir combination therapy was ongoing, a spokesperson told The BMJ.

How much does Paxlovid cost?

In the US, a five day course costs $529 (£410; €490), according to the independent US non-profit Institute for Clinical and Economic Review. It estimated that this equated to $21 000 per hospital admission averted in that country.

What’s the potential for this drug?

Paxlovid should be used “as part of a comprehensive strategy for vaccination, testing, and rapid treatment for patients at higher risk of progressing to more serious covid-19,” Steve Pearson, president of the Institute for Clinical and Economic Review, told The BMJ. “The key feature of the oral treatments is that they may help make administration of rapid treatment more feasible across different types of healthcare settings,” he added. Like any antimicrobial drug, including antibiotics, relying too heavily on Paxlovid increases the chances that SARS-CoV-2 will evolve to become resistant. WHO’s spokesperson agreed, saying, “Prevention is better than cure. Even if proved safe and effective, antiviral drugs will not be alternatives to vaccines.”

Competing interests: I have read and understood the BMJ policy on declaration of interests and have no relevant interests to declare.

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