TOURO COLLEGE OF PHARMACY
DRUG INFORMATION SERVICE

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Dear Dean Cohen,

Thank you for your questions regarding the pharmacology and trials supporting molnupiravir and Paxlovid for COVID-19 treatment.

This response consists of two main sections. The first section is a summary of the overall response, and the second section contains detailed response to your questions.

Section I. Summary of overall evidence

Paxlovid and molnupiravir were both granted FDA EUA status in December 2021 for the treatment of COVID-19. Both medications are designed to inhibit viral replication through their respective mechanisms of action. The clinical trial interim analysis supporting Paxlovid determined that those treated with Paxlovid were 88% less likely to meet the primary outcome of COVID-19 related hospitalization or death from any cause through Day 28. Interim analysis data supporting the authorization of malnupiravir determined that those treated with malnupiravir were 48% less likely to meet the primary outcome of all-cause hospitalization for ≥24 hours or death through Day 29. Data from the all-randomized analysis shows less of a difference for a variety of possible reasons. Data collection on both studies is ongoing. However, both interim analyses met the superiority criterion that led to their authorization for emergency use by the FDA.

Section II. Response

Paxlovid (nirmatrelvir and ritonavir) was granted Emergency Use Authorization (EUA) on December 22, 2021 by the U.S. Food and Drug Administration (FDA) as the first available oral the treatment of COVID-19. Paxlovid tablets are a single use co-packaged oral medication manufactured by Pfizer. Based on the EUA, Paxlovid is indicated for the treatment of mild to moderate COVID-19 in pediatrics (12 years and older weighing at least 40 kg) and COVID-19 positive adults who are at high-risk of progression to severe COVID-19. This medication is only available with a prescription and should be initiated within five days of symptom onset.[1]

The two components within Paxlovid are nirmatrelvir and ritonavir. Nirmatrelvir inhibits the SARS-CoV-2 main protease (Mpro), also referred to as 3C-like protease (3CLpro) or nsp5 protease. This action makes the virus incapable of processing polyprotein precursors thereby preventing viral replication. Ritonavir is a protease inhibitor but is not active against SARS-CoV-2 Mpro. Ritonavir increases the plasma concentrations of nirmatrelvir by inhibiting the CYP3A-mediated metabolism of nirmatrelvir in the body.[2]

The FDA's decision to grant Paxlovid EUA was based on results from the EPIC-HR trial. This trial was a randomized, double-blind, placebo-controlled, 24-week trial that evaluated the safety and efficacy of Paxlovid in the treatment of non-hospitalized adults with COVID-19 at increased risk of developing severe disease. Study participants were ≥18 years old, within five days of confirmed and symptomatic

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COVID-19, and had at least one medical condition associated with increased risk of severe illness development. Those randomized to treatment arm, received the intervention twice daily for five days. Patients who were vaccinated or had a prior COVID-19 infection were excluded.[2]

The primary endpoint was COVID-19 related hospitalization or death from any cause through Day 28. Important secondary outcomes included incidence of adverse events (AEs) through day 34, incidence of treatment emergent adverse events (TEAEs) through day 34, duration and severity of each COVID-19 symptom through day 28, mortality rate through week 24, viral titers through day 14, number of COVID-related medical visits other than hospitalization and number of days of hospitalization or intensive care unit (ICU) treatment through day 34.[3]

A total of 2,246 participants were randomized. Patients who had received or were expected to receive monoclonal antibody treatment (6%) were excluded from the modified intention-to-treat analyses (mITT). Available study results from a scheduled interim analysis indicate a relative risk reduction of 88% in favor of Paxlovid as compared to placebo. The primary outcome was reached in 0.8% (n=8) patients receiving Paxlovid as compared to 6.3% (n=66) patients in the placebo group (Risk reduction -5.62; 95% CI [-7.21 to -4.03]). Through day 28, no deaths were reported in the treatment group as compared to 12 (1.1%) deaths in the placebo group. Adverse events that occurred more frequently in the Paxlovid group as compared to placebo included dysgeusia (altered taste), diarrhea, hypertension, and myalgia. Fewer participants discontinued treatment due to adverse events in the Paxlovid group (2%) as compared to placebo (4%).[2]

Though the efficacy and safety of this new medication is continuing to be evaluated, this trial met the initial criteria for efficacy and safety in COVID-19 patients and lead to the FDA's decision to grant this drug EUA.[1]

Molnupiravir

A second orally administered COVID-19 treatment, molnupiravir, was granted EUA by the FDA on December 23, 2021. Molnupiravir is indicated for the treatment of mild to moderate COVID-19 in adults who are at high-risk for disease progression, and for whom alternative authorized treatments are not accessible or clinically appropriate.[4]

Molnupiravir is a prodrug that gets metabolized to the cytidine nucleoside analogue, β-D-N-Hydroxycytidine (NHC) which is then phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). This molecule gets incorporated into SARS-CoV-2 RNA resulting in genomic errors that disable viral replication.[5]

The FDA decision to grant EUA status to molnupiravir was based on submitted data from the MOVe-OUT trial. This was a randomized, double-blind, phase-3, clinical trial that evaluated molnupiravir in the treatment of non-hospitalized patients with mild to moderate COVID-19 who are at high-risk of disease progression.[2]

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The trial consisted of 1,433 patient that were randomized. The patients enrolled were not hospitalized, had mild to moderate COVID-19 symptoms, confirmed COVID-19 ≤5 days prior to randomization, ≥18 years old, with at least one risk factors for progressing to severe COVID-19. The risk factors included active cancer, COPD, being over the age of 60 years, diabetes, obesity, CKD, serious heart conditions. Patients vaccinated against COVID-19 were excluded from the trial. Participants either received an oral placebo or 800 mg of Molnupiravir by mouth twice a day for 5 days. The primary endpoint in this study was all-cause hospitalization for ≥24 hours or death through Day 29. Secondary endpoints included improvement or progression of COVID-19 signs and symptoms based on the WHO Clinical Progression Scale, and time to resolution or progression of symptoms. Safety outcome analysis included an evaluation of adverse events. A scheduled interim analysis was conducted that included data from 775 of the participants.[6]

The number of participants in the molnupiravir group who met the primary outcome criteria at the time of the interim analysis (7.3% [28 out of 385]) was significantly lower as compared to placebo (14.1% [53 out of 377]; RRR=48%; p=0.001). In the final analysis, 6.8% of participants met the primary outcome criteria in the molnupiravir group as compared to 9.7% in the placebo group (difference, 3.0%; 95% CI [-5.9 to -0.1]; RRR=30%). This difference between risk reduction in the interim analysis and the all-randomized analysis is mainly attributed to differences in rates of the primary outcome in the placebo group. Investigators propose that may be caused by number of factors including participant demographics, criteria for hospitalization in different countries, as well as the nature of prevalent COVID-19 variants. Another analysis evaluating only those hospitalizations that investigators considered to be COVID-19- related showed that 6.3% of participants receiving molnupiravir were hospitalized for COVID-19 as compared to 9.2% of participants in the placebo group (difference, 2.8%; 95% CI [-5.7 to 0.0]). Time-to-event analysis determined that the primary outcome through day 29 was approximately 31% lower with molnupiravir as compared to placebo (HR=0.69; 95% CI [0.48 to 1.01]). In total, one death was reported in the molnupiravir group (0.1%) as compared to nine deaths in the placebo group (1.3%) and risk of death was lower by 89% (95% CI [14 to 99]) with molnupiravir as compared to placebo. All deaths that occurred were said to be COVID-19 related. Several of the subgroups analyzed showed no statistically significant difference between the two groups (patients with evidence of previous COVID-19 infection, low baseline viral load, or diabetes). The population size in some of these subgroups may have been too small to detect any differences. A higher rate of participants receiving molnupiravir showed improved outcomes and resolution of COVID-19 symptoms based on the WHO Clinical Progression Scale as compared to placebo, while participants receiving molnupiravir were less likely to experience progression of COVID-19 signs and symptoms. The safety analysis determined that rates of at least one adverse event and rates of trial related adverse events were similar between the two groups. No deaths that occurred were linked to the trial medication. The most reported adverse events linked to treatment were diarrhea, nausea, and dizziness and all these effects were reported in <2% of participants taking the active intervention.[6]

There are some patient populations that should be aware of safety concerns with molnupiravir use. This treatment is not authorized for use in patients younger than 18 years of age because it may negatively impact bone and cartilage growth. It also should not be used in pregnant patients as safety has not been

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determined in this population and data from animal reproductive studies indicates that molnupiravir may cause fetal harm. Females of childbearing potential should use reliable birth control during treatment and for four days after the final dose. Additionally, males who are sexually active with females of childbearing potential are advised to use a reliable birth control method during treatment and for at least three months following the final dose.[4]

Please note that this information is intended to assist your clinical decision-making process; however, due to the lack of complete and direct access to patient information, Touro College of Pharmacy Drug Information Service cannot account for clinical progress, status, or changes that may occur during the course of treatment and impact patient outcomes. Any decisions made regarding patient treatment is the sole responsibility of the treating health care provider.

We hope this information is helpful to you. Thank you for contacting the Touro College of Pharmacy Drug Information Service. If we may be of further assistance, please do not hesitate to contact us.

Sincerely,
Touro College of Pharmacy Drug Information Service

References:

1. Coronavirus (COVID-19) update: FDA authorizes first oral antiviral for treatment of COVID-19. Updated December 22, 2021. Accessed January 13, 2021. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19
2. Fact sheet for healthcare providers: emergency use authorization for paxlovid. Updated 1222, 2021. Accessed January 13, 2021. https://www.fda.gov/media/155050/download
3. EPIC-HR: Study of oral PF-07321332/Ritonavir compared with placebo in nonhospitalized high risk adults with COVID-19. ClinicalTrials.gov identifier: NCT04960202. Updated January 12, 2022. February 3, 2022. EPIC-HR: Study of Oral PF-07321332/Ritonavir Compared With Placebo in Nonhospitalized High Risk Adults With COVID-19 - Full Text View - ClinicalTrials.gov
4. Coronavirus (COVID-19) update: FDA authorizes additional oral antiviral for treatment of COVID-19 in certain adults. Updated December 23, 2021. Accessed January 18, 2022. Coronavirus (COVID-19) Update: FDA Authorizes Additional Oral Antiviral for Treatment of COVID-19 in Certain Adults | FDA
5. Fact sheet for healthcare providers: emergency use authorization for molnupiravir. Updated 12 23, 2021. Accessed January 13, 2021. https://www.fda.gov/media/155054/download
6. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients [published online ahead of print, 2021 Dec 16]. N Engl J Med. 2021;NEJMoa2116044. doi:10.1056/NEJMoa2116044