To: **CAHAN San Diego Participants**
Date: **December 23, 2021**
From: **Public Health Services**

Health Advisory Update #46: Coronavirus Disease 2019 (COVID-19) Oral Treatment, Paxlovid.

Key Messages

- The U.S. Food and Drug Administration (FDA) has issued an emergency use authorization (EUA) for Pfizer's Paxlovid (nirmatrelvir/ritonavir).
- Paxlovid is indicated for the treatment of mild-to-moderate coronavirus disease (COVID-19) following direct laboratory confirmation of SARS-CoV-2 infection and should be initiated as soon as possible after diagnosis of COVID-19 and within five days of symptom onset.
- Available by prescription only, Paxlovid is for patients ≥12 years of age (weighing least 40 kilograms/88 pounds).
- The U.S. Department of Health and Human Services (HHS) will be distributing allocations. In San Diego County, Paxlovid will be available in limited supply at state-specified pharmacies beginning the first week of January 2022.

Situation

Background
On December 22, 2021, the U.S. Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for Pfizer's Paxlovid (nirmatrelvir/ritonavir). On December 23, 2021, the California Department of Public Health (CDPH) issued the accompanying health alert with additional information and guidance on Paxlovid.

Paxlovid (nirmatrelvir 300 mg and ritonavir 100 mg, co-packaged)
- Statistically significantly reduced all-cause hospitalizations compared to placebo (0.8% vs. 6.3%) and also reduced all-cause deaths (0 vs. 1.1%) through day 28.
- Available by prescription only.
- Administered orally (to be taken together) twice daily for 5 days for the treatment COVID-19.
- Authorized for use in adults and pediatric patients (≥12 years and weighing at least 40 kilograms/88 pounds).
- Indicated for eligible persons with positive molecular SARS-CoV-2 testing and at high risk for progression to severe COVID-19, including hospitalization or death (for specific medical conditions and factors: People with Certain Medical Conditions).
- Should be initiated as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset.
- Not authorized for initiation of treatment in patients who already require hospitalization
  - Patients requiring hospitalization after starting treatment may complete the full 5-day treatment course per the healthcare provider's discretion.
- Not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
- Possible side effects include impaired sense of taste, diarrhea, high blood pressure, and muscle aches.
- May lead to HIV-1 drug resistance in patients with uncontrolled or undiagnosed HIV-1 infection.
- Ritonavir may cause liver damage. Exercise caution with preexisting liver diseases, liver enzyme abnormalities, or liver inflammation.

- Not recommended in patients with severe kidney or severe liver impairment.
- Patients with moderate renal impairment may require a reduced dosing.

Distribution

The U.S. Department of Health and Human Services (HHS) Office of the Assistant Secretary for Preparedness and Response (ASPR) announced it will oversee the fair and equitable allocation of Paxlovid to state and territorial health departments and select Health Resources & Services Administration (HRSA) funded health clinics. In San Diego County, initial courses of Paxlovid will begin arriving during the first week of January at state-selected Rite Aid and CVS pharmacies.

Actions Requested

1. Remain up-to-date on COVID-19 vaccine with the indications for Paxlovid including the conditions that place individuals at higher risk for more severe disease.
2. In eligible patients, begin treatment as soon as possible and within 5 days of symptom onset.
3. Only prescribe as directed taking into account contraindications and precautions.
4. Report all serious medication errors and adverse events that are considered to be potentially attributable to Paxlovid by completing and a MedWatch form, or completing and submitting FDA Form 3500 (health professional) by fax (1-800-FDA-0178). Call 1- 800-FDA-1088 for questions.

Resources

- Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid (fda.gov)
- Fact Sheet for Patients, Parents, and Caregivers: Emergency Use Authorization of Paxlovid (fda.gov)
- Frequently Asked Questions on the Emergency Use Authorization for Paxlovid (fda.gov)

Thank you for your participation.

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Health Alert
Authorization of Paxlovid for Treatment of Mild to Moderate COVID-19, Distribution, Patient Prioritization, and Ethical Considerations
December 23, 2021

Background

On 22 December 2021, the U.S. Food and Drug Administration (FDA) issued an emergency use authorization (EUA)[1] for Pfizer's Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) for the treatment of mild-to-moderate coronavirus disease (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kilograms).

On December 14, 2021, Pfizer had announced the results from an analysis of 2,246 adults who received either Paxlovid or placebo enrolled in its Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR)[2] trial. Patients were adults 18 years of age and older with a risk factor for progression to severe disease or were 60 years and older regardless of prespecified chronic medical conditions. All patients had not received a COVID-19 vaccine and had not been previously infected with COVID-19. In the study, Paxlovid significantly reduced the proportion of people with COVID-19 related hospitalization or death from any cause by 88% compared to placebo among patients treated within five days of symptom onset.

Authorization for Use and Clinical Considerations

The EUA[3] for Paxlovid authorizes use for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with:

- Positive results of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing; **AND**
- Who are at high risk for progression to severe COVID-19, including hospitalization or death.

Paxlovid may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which Paxlovid belongs (i.e., antiinfectives).

Paxlovid is not authorized for the pre-exposure or post-exposure prevention of COVID-19 or for initiation of treatment in those requiring hospitalization due to severe or critical COVID-19. Paxlovid is not a substitute for COVID-19 vaccination.

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[1] https://www.fda.gov/media/155049/download; https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19
[2] https://clinicaltrials.gov/ct2/show/NCT04960202
[3] https://www.fda.gov/media/155050/download

Healthcare providers should review the EUA prior to prescribing Paxlovid. Healthcare providers should consider the potential for drug interactions prior to and during Paxlovid therapy and review concomitant medications during Paxlovid therapy. Paxlovid is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions. A list of potential medications that might lead to drug interactions is included in the product EUA.

Paxlovid Allocation and Expected Quantity

The federal government will be allocating Paxlovid to states, and the California Department of Public Health (CDPH) will allocate Paxlovid to jurisdictions based on new COVID-19 cases and an equity measure. The equity measure in the formula will be based on zip-code-level Healthy Places Index (HPI) Scores.

Within each jurisdiction, Paxlovid will be distributed to selected providers and pharmacies who can dispense medications selected by Local Health Jurisdictions to distribute equitably. During the initial weeks of allocation, when supplies of Paxlovid remain scarce, only a few providers and pharmacies in each jurisdiction will be receiving product. Patients will require a prescription for Paxlovid and should be directed to sites that have received Paxlovid.

Overall supply in the initial weeks that the drug is available is expected to be extremely limited. The U.S. Department of Health and Human Services has announced that only 64,970 treatment courses will be available to the entire United States, with 6,180 courses allocated to California. Further federal allocations are not expected again until early January 2022.

As COVID-19 cases increase due to Omicron around the state, demand for Paxlovid is expected to exceed available supply.

Prioritization of Patients for Paxlovid

Given the limited amount of Paxlovid available, product scarcity is expected.

While the National Institutes of Health (NIH) treatment guidelines[4] listing priority groups for treatment with anti-SARS-CoV-2 monoclonal antibodies were not written for oral anti-virals like Paxlovid, the criteria set out by NIH can be used to prioritize patients getting Paxlovid when product is limited:

- Treatment should be prioritized in unvaccinated or incompletely vaccinated individuals and vaccinated individuals who are not expected to mount an adequate immune response (e.g., individuals who are immunocompromised or on immunosuppressive medications or individuals aged ≥65 years).

[4] https://www.covid19treatmentguidelines.nih.gov/therapies/updated-statement-on-the-prioritization-of-anti-sars-cov-2-mabs/

Patients should only receive Paxlovid if they have symptomatic disease meeting the criteria as defined by the NIH[5]:

- *Mild Illness:* Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.
- *Moderate Illness:* Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO_2) ≥94% on room air at sea level.

Further prioritization will be needed until we begin to receive more adequate supply. CDPH recommends additionally prioritizing high-risk patients with *moderate illness* as defined above in the following order:

1. Immunocompromised or on immunosuppressive medications
2. Incompletely vaccinated AND > 65 years of age with risk factors for severe disease
3. > 65 years of age with risk factors for severe disease

The Centers for Disease Control and Prevention (CDC) provides a list of risk factors[6] for severe COVID-19. Some of the most important risk factors include (listed alphabetically): age (risk increases with each decade after age 50)[7], cancer, cardiovascular disease, chronic kidney disease, chronic lung disease, diabetes, immunocompromising conditions or receipt of immunosuppressive medications, obesity (body mass index ≥30), pregnancy, and sickle cell disease.

For a complete list of risk factors, including information on the relative risk of severe disease, see the CDC webpage "Underlying Medical Conditions Associated with High Risk for Severe COVID-19"[8]. Of note, the likelihood of developing severe COVID-19 increases when a person has multiple comorbidities.[9]

Although the data on risk factors for severe COVID-19 in children are limited, there is substantial overlap between risk factors in children and those identified in adults, as listed above. Children with obesity, moderate to severe immunosuppression, or those with complex chronic disease and medical complexity with respiratory technology dependence are at substantially increased risk of severe disease.[10] Paxlovid is only authorized for use in children over 12 years of age and weighing at least 40 kg.

Ethical Considerations

Supplies of Paxlovid are expected to be limited. The overall aim in distribution and use of Paxlovid should be to achieve the greatest overall clinical benefit to patients infected with COVID-19, avoid bias, and mitigate healthcare disparities.

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[5] https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/
[6] https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/underlying-evidence-table.html
[7] https://www.cdc.gov/aging/covid19/covid19-older-adults.html
[8] https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html
[9] https://www.ncbi.nlm.nih.gov/pubmed/33301018.
[10] https://www.ncbi.nlm.nih.gov/pubmed/34097050.

Clinicians are likely to find that they do not have adequate Paxlovid supply for all eligible patients initially. This situation will be challenging for patients and family members, clinicians, and hospital staff. As outlined in the Guidance for Hospitals Regarding Allocation of Scarce Medications for COVID-19, CDPH recommends[11]:

- Establishing a multidisciplinary evidence-based clinical prioritization committee, including representatives from specialties involved in the care of patients eligible for Paxlovid as well as, if available, administration, pharmacy, ethics, and infectious disease.
- Developing healthcare system guidelines for appropriate use of Paxlovid which adhere to the product EUA and reflect the patient population.

The four fundamental principles of ethics (autonomy, beneficence, nonmaleficence, and justice) should be incorporated into all decision-making regarding resource allocation.

[11] https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/COVID-19/GuidanceForHospitalsRegardingAllocationOfScarceMedicationsForCOVID19.aspx