



TOMÁS J. ARAGÓN, M.D., Dr.P.H.
Director and State Public Health Officer

State of California—Health and Human Services Agency
California Department of Public Health



GAVIN NEWSOM
Governor

Health Alert
Authorization of Molnupiravir for Treatment of Mild to Moderate COVID-19, Distribution, Patient Prioritization, and Ethical Considerations
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Background

On 23 December 2021, the U.S. Food and Drug Administration (FDA) issued an emergency use authorization (EUA)¹ for Merck's Molnupiravir for the treatment of mild-to-moderate coronavirus disease (COVID-19) in adults (18 years of age and older)². Molnupiravir is authorized for use in situations where other FDA-authorized treatments for COVID-19 are inaccessible or are not clinically appropriate.

Molnupiravir is a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis. On December 16, 2021, Merck published the Phase 3 results from the MOVE-OUT trial^{3,4} a double-blind, randomized placebo-control trial of 1,433 patients. Enrolled participants had not received a COVID-19 vaccination and had at least one risk factor associated with poor disease outcomes and symptom onset within five days prior to study enrollment. The risk of hospitalization for any cause or death through day 29 was lower with Molnupiravir (6.8%) than with placebo (9.7%), for a relative risk reduction of 30% and absolute risk reduction of 3.0%. One death was reported in the Molnupiravir groups and 9 in the placebo group through day 29.

Authorization for Use and Clinical Considerations

The EUA for Molnupiravir authorizes use for the treatment of mild-to-moderate COVID-19 in adult patients (18 years of age and older) 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; **AND**
- For whom other FDA-authorized treatments for COVID-19 are inaccessible or are not clinically appropriate

Molnupiravir may only be prescribed for an individual patient by physicians, advanced

¹ <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-oral-antiviral-treatment-covid-19-certain>

² <https://www.fda.gov/media/155054/download>

³ <https://clinicaltrials.gov/ct2/show/NCT04575597>

⁴ <https://www.merck.com/news/merck-and-ridgeback-announce-publication-of-phase-3-study-of-molnupiravir-an-investigational-oral-antiviral-covid-19-treatment-in-the-new-england-journal-of-medicine/>

practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which Molnupiravir belongs (i.e., anti-infectives).

Molnupiravir is not authorized for use in patients younger than 18 years of age because it may affect bone and cartilage formation and growth. Molnupiravir 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. Molnupiravir is not a substitute for COVID-19 vaccination.

Healthcare providers should review the EUA prior to prescribing Molnupiravir and should consider the potential risks/benefits to prescribing Molnupiravir.

Based on findings from animal reproduction studies, Molnupiravir may cause fetal harm when administered to pregnant individuals and Molnupiravir is not recommended for use during pregnancy or breastfeeding. Females of childbearing potential are advised to use a reliable method of birth control during treatment with Molnupiravir and for four days after the final dose. Breastfeeding is not recommended during treatment and for 4 days after the last dose of Molnupiravir. Males of reproductive potential who are sexually active with females of childbearing potential are advised to use a reliable method of birth control during treatment and for at least three months after the final dose.

Molnupiravir Allocation and Expected Quantity

The federal government will be allocating Molnupiravir to states, and the California Department of Public Health (CDPH) will allocate Molnupiravir 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, Molnupiravir will be distributed to providers and pharmacies who can dispense medication selected by Local Health Jurisdictions to distribute equitably. During the initial weeks of allocation, when supplies of Molnupiravir remain low, only a few pharmacies in each jurisdiction will be receiving product. Patients will require a prescription for Molnupiravir and should be directed to pharmacies that have received Molnupiravir.

Overall supply in the initial weeks that the drug is available is expected to be limited, with U.S. Department of Health and Human Services allocating 28,920 courses to California in late December. Further federal allocations are not expected again until early January 2022.

In the setting of likely increasing COVID-19 cases due to Omicron around the state, demand for FDA authorized outpatient COVID-19 treatments, including Molnupiravir, may exceed available supply.

Eligibility of Patients for Molnupiravir

Patients should only receive Molnupiravir if they have symptomatic disease meeting the criteria as defined by the NIH⁵:

- 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 (SpO₂) $\geq 94\%$ on room air at sea level.

Because of its lower effectiveness, Molnupiravir should not be used for treatment in patients where any of the below therapies are accessible and clinically appropriate:

- Paxlovid, 300 mg nirmatrelvir with 100 mg ritonavir, taken together twice daily for 5 days; administered as soon as possible and within 5 days of symptom onset;
- OR**
- An FDA authorized anti-SARS-CoV-2 monoclonal antibody, in areas where Omiron makes up $\geq 20\%$ of infections, Sotrovimab 500 mg IV as a single infusion administered as soon as possible and within 10 days of symptom onset should be used

Additionally, while currently an off-label use from its FDA approved indication, daily intravenous administration of Remdesivir for three days initiated within seven days of symptom onset⁶ can be considered and is now included on the National Institutes of Health (NIH) treatment guidelines⁷ as an option for outpatients with mild to moderate symptoms.

While the National Institutes of Health (NIH) treatment guidelines⁸ listing priority groups for treatment with anti-SARS-CoV-2 monoclonal antibodies were not written for oral anti-virals like Molnupiravir, the criteria set out by NIH can be used to prioritize patients getting Molnupiravir 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).

⁵ <https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/>

⁶ <https://www.nejm.org/doi/full/10.1056/NEJMoa2116846>

⁷ <https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-anti-sars-cov-2-mabs-and-rdv-and-omicron/>

⁸ <https://www.covid19treatmentguidelines.nih.gov/therapies/updated-statement-on-the-prioritization-of-anti-sars-cov-2-mabs/>

If supply remains limited after applying the above criteria, 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 factors⁹ for severe COVID-19. Some of the most important risk factors include (listed alphabetically): age (risk increases with each decade after age 50)¹⁰, 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”¹¹. Of note, the likelihood of developing severe COVID-19 increases when a person has multiple comorbidities.¹²

Ethical Considerations

Supplies of FDA authorized therapeutics to treat outpatients for COVID-19 are expected to be limited. The overall aim in distribution and use of FDA authorized outpatient therapies should be to achieve the greatest overall clinical benefit to patients infected with COVID-19, avoid bias, and mitigate healthcare disparities.

Shortages 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 recommends¹³:

- Establishing a multidisciplinary evidence-based clinical prioritization committee, including representatives from specialties involved in the care of patients eligible for outpatient COVID-19 treatments as well as, if available, administration, pharmacy, ethics, and infectious disease.
- Developing healthcare system guidelines for appropriate use of outpatient treatments which adhere to the product EUAs 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.

⁹ <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/underlying-evidence-table.html>

¹⁰ <https://www.cdc.gov/aging/covid19/covid19-older-adults.html>

¹¹ <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html>

¹² <https://www.ncbi.nlm.nih.gov/pubmed/33301018>.

¹³ <https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/COVID-19/GuidanceForHospitalsRegardingAllocationOfScarceMedicationsForCOVID19.aspx>