

# Molnupiravir

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Molnupiravir is the oral prodrug of beta-D-N4-hydroxycytidine (NHC), a ribonucleoside that has shown antiviral activity against SARS-CoV-2 in vitro and in some clinical trials.<sup>1,2</sup> NHC uptake by viral RNA-dependent RNA-polymerases results in viral mutations and lethal mutagenesis.<sup>3,4</sup> On December 23, 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for molnupiravir for the treatment of adults with mild to moderate COVID-19 who are within 5 days of symptom onset, who are at high risk of progressing to severe disease, and for whom alternative antiviral therapies are not accessible or clinically appropriate.<sup>5,6</sup> Molnupiravir is expected to be active against the Omicron variant and its subvariants.<sup>6</sup>

There is a theoretical risk that the molnupiravir metabolite NHC could be incorporated into the host DNA, leading to mutations. The available genotoxicity data and the 5-day duration of treatment led the FDA to conclude that molnupiravir has a low risk for genotoxicity.

## Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using **molnupiravir 800 mg** orally (PO) twice daily for 5 days as an alternative therapy in nonhospitalized patients aged  $\geq 18$  years with mild to moderate COVID-19 who are at high risk of disease progression when ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir are not available, feasible to use, or clinically appropriate; treatment should be initiated as soon as possible and within 5 days of symptom onset (**CIIa**).
- The Panel **recommends against** the use of **molnupiravir** for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated (**AIII**). For more details, see Considerations in Pregnant and Lactating People below.
- People who engage in sexual activity that may result in conception should use effective contraception during and following treatment with molnupiravir. For more details, see Considerations in Sexually Active Individuals below.

Molnupiravir may be used in patients who are hospitalized for a diagnosis other than COVID-19, provided they have mild to moderate COVID-19 and are at high risk of progressing to severe disease. For the Panel's recommendations on preferred and alternative antiviral therapies for outpatients with COVID-19, see [Therapeutic Management of Nonhospitalized Adults With COVID-19](#).

## Rationale

The MOVE-OUT trial enrolled high-risk, unvaccinated, nonhospitalized adults and reported that molnupiravir reduced the rate of hospitalization or death among these patients by 31% compared to placebo.<sup>7</sup> A secondary analysis of patients who required hospitalization during the trial found a reduced need for respiratory interventions among those who received molnupiravir compared to those who received placebo.<sup>8</sup> MOVE-OUT was conducted before the emergence of the Omicron subvariants.

The PANORAMIC trial enrolled nonhospitalized adults with COVID-19 who were at high risk of severe disease during a period when the Omicron variant was circulating.<sup>9</sup> Ninety-four percent of the patients had received at least 3 doses of a COVID-19 vaccine. The study found that the use of molnupiravir plus usual care did not reduce the occurrence of the primary composite outcome of hospitalization or death

compared to usual care alone. The proportion of patients who met this composite outcome was 1% in both arms. Molnupiravir plus usual care was superior to usual care alone for several secondary clinical endpoints. For example, the time to self-reported recovery was substantially shorter in people who received molnupiravir plus usual care than in people who received usual care alone (median of 9 days vs. 15 days). Because the PANORAMIC trial was an open-label study with self-reported symptoms, the findings are less reliable than those from a placebo-controlled trial.

For more information on the MOVE-Out and PANORAMIC trials, see the Clinical Data section below.

Although the different COVID-19 treatment options have not been directly compared in clinical trials, the Panel recommends using **molnupiravir** only when ritonavir-boosted nirmatrelvir and remdesivir are not available, feasible to use, or clinically appropriate (**CIIa**). Molnupiravir appears to have lower clinical efficacy than these other treatment options.

Some observational studies have evaluated the use of molnupiravir in nonhospitalized or hospitalized adults who are at high risk of progressing to severe disease, including some patients who received COVID-19 vaccines, but these studies have limitations.<sup>10-12</sup> For treatment considerations for vaccinated individuals, see [Therapeutic Management of Nonhospitalized Adults With COVID-19](#).

### Additional Considerations

- Patients should complete the 5-day treatment course of molnupiravir. It is unknown whether a shorter course is less effective or associated with the emergence of molnupiravir-resistant mutations.
- If a patient requires hospitalization after starting treatment, the full treatment course of molnupiravir can be completed at the health care provider's discretion.
- The FDA EUA for molnupiravir provides instructions for preparing and administering capsule contents through orogastric or nasogastric tubes.<sup>6</sup>
- There are no data on using combinations of antiviral therapies to treat nonhospitalized patients with COVID-19. Clinical trials are needed to determine whether combination therapy has a role in the treatment of SARS-CoV-2 infection.
- Patients who are severely immunocompromised can experience prolonged periods of SARS-CoV-2 replication, which may lead to rapid viral evolution. There are theoretical concerns that using a single antiviral agent in these patients may produce antiviral-resistant viruses. Additional studies are needed to assess this risk. The role of combination antiviral therapy in treating patients who are severely immunocompromised is not yet known. See [Special Considerations in People Who Are Immunocompromised](#) for more information.
- There are limited data on the frequency of SARS-CoV-2 rebound in patients who have completed treatment with molnupiravir.<sup>13</sup> During the MOVE-OUT trial, rates of symptomatic SARS-CoV-2 rebound were low (approximately 1%) in both those who received molnupiravir and those who received placebo.<sup>6</sup>
- SARS-CoV-2 sequences with molnupiravir-induced mutations have been detected in many countries, but the clinical implications of these mutations remain unclear.<sup>14</sup>

### Monitoring, Adverse Effects, and Drug-Drug Interactions

The most common adverse effects of molnupiravir are diarrhea, nausea, and dizziness. Based on in vitro studies, neither molnupiravir nor its active metabolite NHC are inhibitors or inducers of major drug-metabolizing enzymes or inhibitors of major drug transporters.

According to the FDA EUA, no drug-drug interactions have been identified for molnupiravir.

## Considerations in Sexually Active Individuals

For individuals of childbearing potential, clinicians should assess the patient's pregnancy status before initiating molnupiravir.

Patients of childbearing potential should be counseled about abstaining from sex or using reliable contraception for the duration of therapy and for up to 4 days after taking molnupiravir. Reproductive toxicity has been reported in animal studies of molnupiravir, and molnupiravir may be mutagenic during pregnancy.

The FDA EUA states that men of reproductive potential who are sexually active with individuals of childbearing potential should be counseled to abstain from sex or use a reliable method of contraception for the duration of treatment and for at least 3 months after the last dose of molnupiravir.

## Considerations in Pregnant and Lactating People

The Panel **recommends against** the use of **molnupiravir** for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated (**AIII**). Because the risk of adverse effects in infants is currently unknown, the FDA EUA fact sheet does not recommend feeding an infant breast milk from a patient who is taking molnupiravir for the duration of the treatment course and until 4 days after the final dose. See [Pregnancy, Lactation, and COVID-19 Therapeutics](#) for more information.

## Considerations in Children

The MOVE-OUT and PANORAMIC trials excluded participants aged <18 years. There are no data available on the use of molnupiravir in children aged <18 years. Molnupiravir is not authorized for use in those aged <18 years due to potential effects on bone and cartilage growth.

## Clinical Data

### *MOVE-OUT*

MOVE-OUT was a Phase 3 trial that evaluated the use of molnupiravir in unvaccinated, nonhospitalized adults with mild to moderate COVID-19 who were at high risk of progressing to severe COVID-19 and who were enrolled within 5 days of symptom onset.<sup>7</sup> Patients were randomized to receive molnupiravir 800 mg PO every 12 hours for 5 days or placebo. The primary composite endpoint was a hospital stay >24 hours or death by Day 29.

### Results

- The final analysis included 1,433 patients.
  - The median age was 43 years (with 17% aged >60 years); 49% of patients were men, 57% were White, 50% were Hispanic/Latinx, and 5% were Black or African American.
  - 4% had a body mass index  $\geq 30$ , and 16% had diabetes.
- The time from the onset of COVID-19 symptoms to randomization was  $\leq 3$  days in 48% of patients.
- By Day 29, 48 of 709 patients (6.8%) in the molnupiravir arm and 68 of 699 (9.7%) in the placebo arm experienced hospitalization or death (adjusted difference -3.0%; 95% CI, -5.9% to -0.1%).
- One death occurred in the molnupiravir arm, and 9 deaths occurred in the placebo arm.

- There were no significant differences between the arms in the proportions of patients who experienced adverse events.
- A secondary analysis of data from the patients who were hospitalized during the trial revealed that the use of molnupiravir reduced the risk of requiring respiratory interventions (conventional or high-flow oxygen delivery, noninvasive ventilation, or mechanical ventilation) by 21%.<sup>8</sup>

### Limitations

- This study was conducted before the emergence of the Omicron variant and its subvariants.

## PANORAMIC

PANORAMIC was a multicenter, open-label, adaptive platform trial conducted in the United Kingdom that evaluated the use of molnupiravir in nonhospitalized adults who were at high risk of progressing to severe COVID-19.<sup>9</sup> The participants were aged  $\geq 50$  years or  $\geq 18$  years with comorbid conditions and were enrolled within 5 days of symptom onset. Patients were randomized to receive molnupiravir 800 mg PO twice daily for 5 days plus usual care or usual care alone. The primary endpoint was a composite of all-cause hospitalization (defined as  $\geq 1$  overnight hospital stay,  $\geq 1$  night at home with care and monitoring by hospital clinicians, or an overnight stay in an emergency room) or death within 28 days. The trial was conducted when the Omicron variant was the dominant variant.

### Results

- The final analysis included 25,708 patients.
  - The mean age was 56.6 years (26.5% aged  $\geq 65$  years); 94% were White; 59% were women.
  - 94% received  $\geq 3$  doses of a COVID-19 vaccine.
  - 69% of patients had comorbidities: 25% with lung disease; 15% with obesity; 12% with diabetes; 8% with heart disease; 8.5% were immunocompromised.
  - 24% were taking inhaled corticosteroids.
- The mean time from symptom onset to starting molnupiravir was 3 days (range 3–5 days). Among the patients who provided information, 95% reported completing the 5-day treatment course.
- The study reported 103 hospitalizations and 3 deaths in the molnupiravir arm and 96 hospitalizations and 5 deaths in the usual care alone arm (aOR 1.06; 95% CrI, 0.81–1.41; probability of superiority 0.33).
- The time to self-reported first recovery among those who received molnupiravir (median of 9 days) was shorter than among those who received usual care alone (median of 15 days).
- No serious adverse events were related to molnupiravir; 145 patients (1.1%) withdrew because of adverse events attributed to molnupiravir.

### Limitations

- Because the PANORAMIC trial was an open-label study and the patients knew whether they were receiving molnupiravir or not, this may have affected their reported symptoms. As a result, these findings are less reliable than those from a placebo-controlled trial.

## References

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