Molnupiravir

Section last reviewed and updated 12/28/2021

Last literature search conducted 12/28/2021

Recommendation (NEW): In ambulatory patients (≥ 18 years) with mild to moderate COVID-19 at high risk for progression to severe disease who have no other treatment options*, the IDSA guideline panel suggests molnupiravir initiated within 5 days of symptom onset rather than no molnupiravir. (Conditional recommendation, Low certainty of evidence)

Remarks:

- Patients who put a higher value on the putative mutagenesis, adverse events or reproductive concerns, and a lower value on the uncertain benefits, would reasonably decline molnupiravir.
- Molnupiravir 800 mg for 5 days
- Patients with mild to moderate COVID-19 who are at high risk of progression to severe disease admitted to the hospital for reasons other than COVID-19 may also receive molnupiravir.
- Molnupiravir is not authorized under the FDA EUA for use in patients < 18 years, because it may affect bone and cartilage growth.
- Molnupiravir is not recommended under the FDA EUA for use during pregnancy.
- Molnupiravir is not authorized under the FDA EUA for pre-exposure or post-exposure prevention of COVID-19 or for initiation of treatment in patients hospitalized due to COVID-19, because benefit of treatment has not been observed in individuals when treatment is started after hospitalization due to COVID-19.

* Other options for treatment and management of ambulatory patients include nirmatrelvir/ritonavir, three-day treatment with remdesivir, and neutralizing monoclonal antibodies. Patient-specific factors (e.g., symptom duration, renal function, drug interactions) as well as product availability should drive decision-making regarding choice of agent. Data for combination treatment do not exist in this setting.

Reference

**Why is molnupiravir considered for treatment?**

Molnupiravir is an oral antiviral that targets the genetic machinery that is responsible for SARS COV-2 replication. Molnupiravir is an oral pro-drug that is converted to β-D-N4-hydroxycytidine (NHC) which acts as a substrate for RNA-dependent RNA polymerase. After it is incorporated into the viral RNA, serial mutations develop, resulting in a virus that is less fit for ongoing viral replication. One phase 1 RCT evaluated the safety and tolerability of molnupiravir in healthy adults without COVID-19 [1]. The study reported molnupiravir to be well tolerated, with no increased reports of serious adverse events among persons in the molnupiravir arm compared to those receiving placebo. The U.S. Food and Drug Administration (FDA) granted emergency use authorization (EUA) to molnupiravir on December 23, 2021, for the treatment of mild-to-moderate COVID-19 in adults (≥18 years) who are at high risk for progression to severe COVID-19, including hospitalization or death.

**Summary of the evidence**

Two RCTs reported on treatment of unvaccinated patients with COVID-19 with either 800 mg of molnupiravir or placebo for five days [2-3]. In one phase 3 trial (MOVe-OUT trial) reporting on the outcomes of death, hospitalization and serious adverse events, patients with mild-to-moderate COVID-19 received either molnupiravir or placebo within 5 days after the onset of symptoms. In the phase 2a trial reporting on the outcomes of death and serious adverse events in patients with symptom duration <7 days received molnupiravir or placebo.

**Benefits**

COVID-19-related mortality may be lower in patients receiving molnupiravir rather than placebo (RR: 0.11; 95% CI: 0.01, 0.86; low CoE). Similarly, COVID-19-related hospitalizations and the composite of all-cause hospitalization or death may trend towards a reduction among patients receiving molnupiravir rather than no molnupiravir (RR: 0.68; 95% CI: 0.48, 1.00; low CoE and HR: 0.69; 95% CI: 0.48, 1.01; low CoE, respectively).

**Harms**

Patients treated with molnupiravir may not experience greater serious adverse events than those receiving placebo (RR: 0.43; 95% CI: 0.17, 1.11; low CoE).

Based on findings from animal reproduction studies, molnupiravir may cause fetal harm when administered to pregnant individuals [4]. Other concerns with molnupiravir include the possibility of viral mutagenesis in persons with compromised immune systems who are unable to clear the virus. Females of childbearing potential should be counseled to use a reliable method of contraception during treatment and for 4 days after the last dose. Men of reproductive potential who are sexually active with females of childbearing potential should be counseled to use a reliable method of contraception during treatment and for at least three months after the last dose of molnupiravir. It is also not recommended in children <18 years of age for the concern of bone growth.
Molnupiravir does not require renal or hepatic dose adjustment.

Other considerations

The panel agreed that the overall certainty of evidence for treatment of ambulatory patients was low, given concerns with imprecision, driven by few reported events and a relatively small effect.

The use of molnupiravir presents additional considerations and potential concerns regarding viral mutagenesis in immunocompromised persons and safety in persons of reproductive age, for which more data are needed to quantify such effects. The panel recognized that alternative treatment options exist with the possibility of greater benefit with a smaller known safety profile. The FDA required the manufacturers to conduct additional animal studies on the impact of the drug on spermatogenesis and to establish a pregnancy registry if the drug was inadvertently administered during pregnancy.

The evidence confirms that using molnupiravir early in the disease process when viral loads are high confers maximum benefit. It is critical to make a rapid diagnosis and treat ambulatory patients with COVID-19 early in the disease course.

Conclusions

The guideline panel suggests the use of molnupiravir for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease who are within 5 days of symptom onset and have no other treatment options. More data are needed on the potential adverse effects of this medication. The evidence supporting this recommendation will be reassessed with the release of updated published information from the MOVe-OUT study and other trials.
**Question:** Molnupiravir compared to no molnupiravir for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease (v1)

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>№ of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td>COVID-19-related mortality (follow-up: range 28 days to 29 days)</td>
<td>2,\textsuperscript{1,2}</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>COVID-19-related hospitalizations (follow-up: 29 days)</td>
<td>1,\textsuperscript{1}</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Hospitalization or death (all-cause) (follow-up: 29 days)</td>
<td>1,\textsuperscript{1}</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Serious adverse events (follow-up: range 28 days to 29 days)</td>
<td>2,\textsuperscript{1,2}</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
</tbody>
</table>

**GRADE Working Group grades of evidence**

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect
- **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
- **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

**Risk of bias:** Study limitations
- **Inconsistency:** Unexplained heterogeneity across study findings
- **Indirectness:** Applicability or generalizability to the research question
- **Imprecision:** The confidence in the estimate of an effect to support a particular decision
- **Publication bias:** Selective publication of studies
NB: Certainty ratings are derived from evidence that has not been peer reviewed or published.

CI: confidence interval; HR: hazard Ratio; RR: risk ratio

Explanations
a. In Bernal 2021, after day 29, one additional death resulting from adverse events occurred in the molnupiravir group and three additional deaths occurred in the placebo group. In Fischer 2021, at day 31, one additional death resulting from hypoxia occurred in the placebo group.
b. Small number of events; fragility present.
c. 95% CI cannot exclude no meaningful benefit.
d. COVID-19 related hospitalizations is a surrogate for ICU admission, mechanical ventilation and death. Not rated down.
e. All 10 patients reported as died at day 29 had been hospitalized.
f. Small number of events.
g. 95% CI cannot exclude the possibility of harms.

References
References


Supplementary Materials

Study characteristics

- **Table s1.** Molnupiravir vs. no molnupiravir for ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease

Forest Plots

- **Figure s1.** Meta-analysis of molnupiravir on the outcome of mortality
- **Figure s2.** Meta-analysis of molnupiravir on the outcome of serious adverse events

Risk of bias

- **Table s2.** Randomized controlled studies (molnupiravir vs. no molnupiravir)
### Table s1. Molnupiravir vs. no molnupiravir for ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease

<table>
<thead>
<tr>
<th>Study/year</th>
<th>Country/hospital</th>
<th>Study design</th>
<th>N subjects (intervention/comparator)</th>
<th>% female</th>
<th>Age mean (SD)/median (IQR)</th>
<th>Severity of disease</th>
<th>Intervention (study arms)</th>
<th>Comparator</th>
<th>Co-interventions</th>
<th>Outcomes reported</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernal 2021</td>
<td>107 sites in 20 countries</td>
<td>RCT</td>
<td>1433 (716/717)</td>
<td>51.3</td>
<td>43.0 (Range: 18-90)</td>
<td>Ambulatory adults with mild or moderate COVID-19 (at least 1 symptom) with a positive SARS CoV-2 test within 5 days and at least one risk factor for the development of severe disease</td>
<td>Molnupiravir 800 mg twice daily for 5 days</td>
<td>Placebo</td>
<td>Standard of care including: antipyretics, anti-inflammatory agents, glucocorticoids</td>
<td>Mortality, Hospitalization, Rate of hospitalization, Clinical improvement, Serious adverse events</td>
<td>Merck</td>
</tr>
<tr>
<td>Fisher 2021</td>
<td>10 sites in US</td>
<td>RCT</td>
<td>202</td>
<td>51.5</td>
<td>Age: Median (range by treatment arm) Molnupiravir 200 mg: 32 (19-65) Molnupiravir 400 mg: 42.5 (19-82) Molnupiravir 800 mg: 42 (18-68) Placebo: 39 (19-71).</td>
<td>Unvaccinated adults if they had a positive test for SARS CoV-2 infection within 96 hours and had onset of symptoms within 7 days of treatment initiation</td>
<td>Molnupiravir 200 mg every 12 hours x 5 days Molnupiravir 400 mg every 12 hours x 5 days Molnupiravir 800 mg every 12 hours day x 5 days</td>
<td>Placebo</td>
<td>None</td>
<td>Mortality, Change in SARS-CoV-2 viral load from baseline, Median time to COVID-19 symptom resolution, Isolation of infectious virus, SAEs</td>
<td>Merck and Ridgeback Biotherapeutics</td>
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</table>
Figure s1. Meta-analysis of molnupiravir on the outcome of mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Molnupiravir</th>
<th>No molnupiravir</th>
<th>Risk Ratio</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Bernal 2021</td>
<td>1</td>
<td>709</td>
<td>9</td>
</tr>
<tr>
<td>Fischer 2021</td>
<td>0</td>
<td>55</td>
<td>0</td>
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</tbody>
</table>

Total (95% CI) 764 761 100.0% 0.11 [0.01, 0.86]
Risk Ratio: Not estimable
Test for overall effect: Z = 2.10 (P = 0.04)

Figure s2. Meta-analysis of molnupiravir on the outcome of serious adverse events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Molnupiravir</th>
<th>No molnupiravir</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Bernal 2021</td>
<td>5</td>
<td>710</td>
<td>13</td>
</tr>
<tr>
<td>Fischer 2021</td>
<td>1</td>
<td>55</td>
<td>1</td>
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</table>

Total (95% CI) 765 763 100.0% 0.43 [0.17, 1.11]
Risk Ratio: Not estimable
Test for overall effect: Z = 2.10 (P = 0.04)

Table s2. Randomized controlled studies (molnupiravir vs. no molnupiravir)

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessment</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
<th>Other bias</th>
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<tbody>
<tr>
<td>Bernal 2021</td>
<td>Low</td>
<td>High</td>
<td>Unclear</td>
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<td>Fischer 2021</td>
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References for Supplementary Materials
