COVID-19 Therapeutics: Oral Antivirals

MISSISSIPPI STATE DEPARTMENT OF HEALTH
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How to find this presentation on the MSDH website:

[Image of MSDH website navigation menu with highlights on "Coronavirus COVID-19" and "Healthcare Professionals"]

[Image of MS COVID-19 Therapeutics Locator]
Oral Antivirals

• **Paxlovid**: Nirmatrelvir + Ritonavir
  - Nirmatrelvir - a SARS-CoV-2 main protease inhibitor
  - Ritonavir - a CYP3A inhibitor included to increase nirmatrelvir plasma levels
    - Ritonavir alone has no activity against SARS-CoV-2

• **Lagevrio**: Molnupiravir
  - a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis
EUA- Authorized Use

Paxlovid:

• Treatment of mild-to-moderate COVID-19
• Adults and pediatric patients (12 years of age and older weighing at least 40 kg)
• Positive results of direct SARS-CoV-2 viral testing
• High risk for progression to severe COVID-19, including hospitalization or death
  • People with Certain Medical Conditions | CDC
• Must be started within 5 days of symptom onset
• EUA: FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR PAXLOVID (fda.gov)
EUA- Authorized Use

Lagevrio:
• Treatment of mild-to-moderate COVID-19
• Adults (18 years of age and older)
• Positive results of direct SARS-CoV-2 viral testing
• High risk for progression to severe COVID-19, including hospitalization or death
  • People with Certain Medical Conditions | CDC
• Alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate
• Must be started within 5 days of symptom onset
• EUA: FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR MOLNUPIRAVIR (fda.gov)
Limitations of Authorized Use

Paxlovid and Lagevrio are not authorized for:
• Initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19
• Use as pre-exposure or post-exposure prophylaxis for COVID-19
• Use for longer than 5 consecutive days
Efficacy In Clinical Trials

• **Paxlovid:**
  • Reduced COVID-19 related hospitalization and death by 88% when given within 5 days of symptom onset

• **Lagevrio:**
  • Trial P002 (MOVe-OUT): [Efficacy and Safety of Molnupiravir (MK-4482) in Non-Hospitalized Adult Participants With COVID-19 (MK-4482-002) - Full Text View - ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/NCT04311751)
  • Reduced COVID-19 related hospitalization and death by 30% when given within 5 days of symptom onset
Prescribing Requirements

• Paxlovid and Lagevrio require a prescription
• Prescribers must have an encounter with the patient prior to issuing a prescription
  • May be an in-person or virtual encounter
• Include the date of symptom onset on the prescription
  • Must be filled within 5 days of symptom onset
• Patients must be given a copy of the “Fact Sheet for Patients, Parents, and Caregivers”
  • Paxlovid: https://www.fda.gov/media/155051/download
  • Lagevrio: https://www.fda.gov/media/155055/download
Pharmacist Prescribing Requirements for Paxlovid

- Pharmacists may now prescribe Paxlovid under FDA authorization and MSDH standing order
  - MSDH Standing Order: 19176.pdf (ms.gov)
- Patient consultation and counseling must be provided by a licensed pharmacist prior to dispensing Paxlovid.
- Patients must be given a copy of the “Fact Sheet for Patients, Parents, and Caregivers” prior to dispensing Paxlovid.
  - Paxlovid: https://www.fda.gov/media/155051/download
- Pharmacists may NOT prescribe Paxlovid renal dose packs
Dosing

• Begin treatment as soon as possible after COVID-19 diagnosis and within 5 days of symptom onset

• Paxlovid
  • Two 150 mg tablets (300 mg) nirmatrelvir with one 100 mg tablet ritonavir orally twice daily for 5 days
  • May be taken with or without food
  • Dose reduction needed for moderate renal impairment

• Lagevrio
  • Four 200 mg capsules (800 mg) taken every 12 hours for 5 days
  • May be taken with or without food
Safety

Paxlovid:
• Adverse events (incidence ≥1%)
  • dysgeusia (6%)
  • diarrhea (3%)
  • hypertension (1%)
  • myalgia (1%)

Lagevrio:
• Adverse events (incidence ≥1%)
  • diarrhea (2%)
  • nausea (1%)
  • dizziness (1%)
Drug Interactions: Paxlovid

- PAXLOVID (nirmatrelvir co-packaged with ritonavir) is a strong inhibitor of CYP3A and may increase plasma concentrations of drugs that are primarily metabolized by CYP3A. Co-administration of PAXLOVID with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring.

- Nirmatrelvir and ritonavir are CYP3A substrates; therefore, drugs that induce CYP3A may decrease nirmatrelvir and ritonavir plasma concentrations and reduce PAXLOVID therapeutic effect.

- Prescribe alternative COVID-19 therapy for patients receiving any interacting medications that cannot be held during Paxlovid treatment.
Drug Interactions: Paxlovid

For guidance on specific drug-drug interaction management, please refer to:

- Pfizer Paxlovid Fact Sheets for HCPs (07052022) (fda.gov)
- Liverpool COVID-19 Interactions (covid19-druginteractions.org)
- Drug Interaction Checker | Pfizer Medical Information - US
- PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers (fda.gov)
Drug Interactions: Paxlovid

If clinically appropriate, the following medications may be held while the patient is on Paxlovid. If not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy:

<table>
<thead>
<tr>
<th>Medication Category</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Alprazolam, Clonazepam, Diazepam, Triazolam</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Sildenafil, Tadalafil, Vardenafil</td>
</tr>
<tr>
<td>Pain</td>
<td>Codeine, Fentanyl, Hydrocodone, Meperidine, Oxycodone, Tramadol</td>
</tr>
<tr>
<td>Prostate</td>
<td>Alfuzosin, Silodosin, Tamsulosin</td>
</tr>
<tr>
<td>Statins</td>
<td>Atorvastatin, Lovastatin, Rosuvastatin, Simvastatin</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Amlodipine, Diltiazem, Felodipine, Nicardipine, Nifedipine</td>
</tr>
</tbody>
</table>

Drug Interactions: Lagevrio

• No drug interactions have been identified based on the limited data available
### Special Populations: Renal Impairment

**Paxlovid:**

<table>
<thead>
<tr>
<th>eGFR</th>
<th>PAXLOVID Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60 mL/min (normal renal function or mild renal impairment)</td>
<td>300 mg nirmatrelvir with 100 mg ritonavir, taken twice daily for 5 days</td>
</tr>
<tr>
<td>≥30 to ≤60 mL/min (moderate renal impairment)</td>
<td>150 mg nirmatrelvir with 100 mg ritonavir, taken twice daily for 5 days</td>
</tr>
<tr>
<td>&lt;30 mL/min (severe renal impairment)</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

- Pharmacists can dispense the renal dose packaged form of Paxlovid, or,
- Can remove any unneeded tablets and dispose of per the site’s standard policy
  - Instructions for pharmacists and sticker packs accompany each shipment of Paxlovid

**Lagevrio:**

- No adjustment is recommended in patients with any degree of renal impairment
Special Populations: Pregnancy

Paxlovid
• No available clinical data on pregnancy or with breast feeding
• Animal studies showed reduced body weights at ~10x the nirmatrelvir exposure seen in humans with the authorized dose

Lagevrio:
• Not recommended for use during pregnancy
  • Authorized for use in pregnancy only if benefits would outweigh risks for the individual patient
  • Documentation requirements apply
Family Planning Considerations

**Paxlovid**
- Ritonavir may reduce efficacy of combined hormonal contraceptives
  - Patients should use an effective alternative contraceptive method or an additional barrier method of contraception

**Lagevrio**
- Females of childbearing potential should be advised of potential risk to fetus
  - Alternate method of contraception should be used for the duration of the treatment and for 4 days after the last dose
- Males of reproductive potential who are sexually active with women of childbearing potential should use a reliable method of contraception during treatment and for at least 3 months after the last dose
Clinical Decision Tool

- COVID-19 Therapeutics Decision Aid (hhs.gov)
COVID-19 Outpatient Therapeutics
Clinical Decision Aid for Ages 12+

Adult or pediatric patient (ages 12 and older weighing at least 40 kg) with mild to moderate COVID-19 and at high risk for progression to severe disease

Is patient:
• Hospitalized for COVID-19
• Requiring O₂
• Requiring an increase in baseline home O₂ due to COVID-19?

Symptom onset within the past 5–7 days?

Treatment of symptoms, management per NIH & CDC Guidelines

Consider one of the following therapeutics, if available, feasible, and clinically appropriate¹:

Paxlovid² within 5 days of symptom onset If patient does not have severe renal impairment (eGFR <30mL/min OR severe hepatic impairment (Child-Pugh Class C)
  - eGFR ≥ 60 mL/min: 300 mg nirmatrelvir taken with 100 mg ritonavir twice daily for 5 days
  - eGFR 30 to < 60: 150 mg nirmatrelvir taken together with 100 mg ritonavir twice daily for 5 days
  - Evaluate concomitant use of CYP3A inducers and medications with high dependency on CYP3A for clearance as these may be contraindicated²³

  OR

  Veklury (remdesivir)⁴ 200 mg IV x 1 dose on Day 1, 100 mg IV x 1 on Days 2–3 begun ASAP within 7 days of symptom onset

If Paxlovid and Veklury (remdesivir) are not available, feasible or clinically appropriate consider one of the following therapeutics:

beptheadumab⁵ ASAP within 7 days of symptom onset
  175 mg single IV Injection

OR

Lagevrio (molnupiravir)⁶ If patient age 18 or older AND possibility of pregnancy, if applicable, ruled out:
  800 mg by mouth every 12h for 5 days begun ASAP within 5 days of symptom onset

Prescribers must review and comply with the mandatory requirements outlined in the Lagevrio (molnupiravir) EUA⁶

References:
² Paxlovid EUA. https://www.fda.gov/media/135653/download
³ Veklury (remdesivir) EUA. https://www.fda.gov/media/133855/download
⁴ Veklury (remdesivir) Preventing Infection. https://www.fda.gov/media/135652/download
⁵ Beberelumab EUA. https://www.fda.gov/media/133856/download
⁶ Lagevrio (molnupiravir) EUA. https://www.fda.gov/media/132935/download

April 18, 2022

ASPR
Therapeutic Locator

• Sites which dispense oral antivirals can be found on the MSDH website:
  • MS COVID-19 Therapeutics Locator
Paxlovid Shelf-Life Extension

On April 4, 2022, the U.S. Food and Drug Administration (FDA) approved a shelf-life extension for PAXLOVID for lot numbers referenced below.

<table>
<thead>
<tr>
<th>Lot/Batch#</th>
<th>Labeled Expiration date</th>
<th>Extended Expiration Date</th>
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<tbody>
<tr>
<td>FL4516</td>
<td>07/31/22</td>
<td>10/31/22</td>
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<tr>
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<td>FR7229</td>
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<td>10/31/22</td>
</tr>
<tr>
<td>FR9088</td>
<td>08/31/22</td>
<td>11/31/22</td>
</tr>
</tbody>
</table>

How to find this presentation on the MSDH website:
Resources

- Paxlovid Healthcare Provider Fact Sheet: https://www.fda.gov/media/155050/download
- Lagevrio Healthcare Provider Fact Sheet: https://www.fda.gov/media/155054/download
- Trial P002 (MOVe-OUT): Efficacy and Safety of Molnupiravir (MK-4482) in Non-Hospitalized Adult Participants With COVID-19 (MK-4482-002) - Full Text View - ClinicalTrials.gov
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- Therapeutic Locator: https://msdh.ms.gov/msdhsite/_static/14,0,420,694.html - locator
C19therapeutics@msdh.ms.gov

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