COVID-19 Therapeutics: Oral Antivirals

MISSISSIPPI STATE DEPARTMENT OF HEALTH
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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
  • 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
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

Prescribe alternative COVID-19 therapy for patients receiving any of the following:

<table>
<thead>
<tr>
<th>Drug 1</th>
<th>Drug 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Propafenone</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Ranolazine</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Rivaroxaban</td>
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<tr>
<td>Dofetilide</td>
<td>Sildenafil for pulmonary HTN</td>
</tr>
<tr>
<td>Flecaïnide</td>
<td>St. John’s  wort</td>
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<tr>
<td>Phenobarbitol</td>
<td>Tadalafil for pulmonary HTN</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Ticagrelor</td>
</tr>
</tbody>
</table>

For full list see: [Statement on Paxlovid Drug-Drug Interactions | COVID-19 Treatment Guidelines (nih.gov)]
Drug Interactions: Paxlovid

<table>
<thead>
<tr>
<th>Condition</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>
</tbody>
</table>

If withholding any of the following medications is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy:

For full list see: [Statement on Paxlovid Drug-Drug Interactions | COVID-19 Treatment Guidelines (nih.gov)]
Drug Interactions: Paxlovid

- **PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers** (fda.gov)
- **Liverpool COVID-19 Interactions** (covid19-druginteractions.org)
- **Drug Interaction Checker | Pfizer Medical Information - US**
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
  OR
- Requiring O₂
  OR
- Requiring an increase in baseline home O₂ due to COVID-19?
  YES
  NO

Symptom onset within the past 5–7 days?
- NO
  - Treatment of symptoms, management per NIH & CDC Guidelines

- YES
  - Consider one of the following therapeutics, if available, feasible, and clinically appropriate:

    - Paxlovid: 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 contraindicated

    - OR

    - Veklury (remdesivir): 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:

      - bebatermivab: ASAP within 7 days of symptom onset
        - 175 mg single IV Injection

      - OR

      - Lagevrio (molnupiravir): 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) EUA

References:
2. Paxlovid EUA. https://www.fda.gov/media/160510/download
4. Veklury (remdesivir) EUA. https://www.fda.gov/media/165012/download
5. Remdesivir EUA. https://www.fda.gov/media/159264/download

April 18, 2022
Therapeutic Locator

- Sites which dispense oral antivirals can be found on the MSDH website:
  - [MS COVID-19 Therapeutics Locator](http://ms.gov)
  - [17718.pdf (ms.gov)](http://ms.gov)
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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  - Drug Interaction Checker | Pfizer Medical Information - US
- Clinical Decision Tool: COVID-19 Therapeutics Decision Aid (hhs.gov)
- Therapeutic Locator: https://msdh.ms.gov/ MSDHsite_/static/14,0,420,694.html - locator
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