Federal Response to COVID-19: Therapeutics Clinical Implementation Guide

Outpatient Administration Guide for Healthcare Providers

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COVID-19 outpatient therapeutics can be used to prevent or treat eligible non-hospitalized patients who have tested positive for COVID-19 and have mild to moderate symptoms. Prevention and early treatment for eligible patients can help improve patient outcomes, reduce stress on healthcare facilities, and even save lives.

HHS/ASPR has purchased supplies of COVID-19 therapeutic products and is working with state and territorial health departments as well as national healthcare and medical organizations and associations to get the treatments into the hands of healthcare providers quickly, with a focus on areas of the country hardest hit by the pandemic.

This Clinical Implementation Guide summarizes key information on COVID-19 outpatient therapeutics and aims to support healthcare providers’ understanding of these therapies and how to implement their administration.

**IMPORTANT NOTE:** The Clinical Implementation Guide is updated regularly following changes to COVID-19 therapeutics’ Emergency Use Authorizations (EUAs); however, there may be a lag in publishing updated versions. As such, it is important for healthcare providers to stay abreast of the latest changes to EUAs and their impact on the allocation, distribution and administration of COVID-19 therapeutics. See the latest information on all FDA products under EUA. (https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization)
HHS’s COVID-19 Therapeutics Homepage & Announcements

**ASPR’s Response to COVID-19 website:**
https://aspr.hhs.gov/COVID-19/Pages/default.aspx

**New and Notable: COVID-19 Therapeutics Announcements:**
https://aspr.hhs.gov/COVID-19/Therapeutics/Pages/default.aspx
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Module 1:
COVID-19 Outpatient Therapeutics Overview
Who Is At Risk for Severe COVID-19?

COVID-19 Risk Continuum

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>LOWER RISK</th>
<th>HIGHER RISK</th>
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<tbody>
<tr>
<td>&lt;30</td>
<td>1</td>
<td>3+</td>
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<tr>
<td>30–49</td>
<td>2</td>
<td></td>
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<tr>
<td>50–69</td>
<td></td>
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<tr>
<td>≥70</td>
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</table>

<table>
<thead>
<tr>
<th>Medical Conditions (e.g. diabetes, chronic kidney disease, obesity, lung disease, pregnancy)</th>
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</thead>
<tbody>
<tr>
<td>None</td>
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<table>
<thead>
<tr>
<th>Vaccination Status</th>
<th>LOWER RISK</th>
<th>HIGHER RISK</th>
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</thead>
<tbody>
<tr>
<td>Full vaccination plus boosting</td>
<td>1</td>
<td>3+</td>
</tr>
<tr>
<td>Full vaccination</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Partial vaccination</td>
<td>3+</td>
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<tr>
<td>Unvaccinated</td>
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</table>

<table>
<thead>
<tr>
<th>Immunosuppression (Illustrative therapies and conditions)</th>
<th>LOWER RISK</th>
<th>HIGHER RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Corticosteroids</td>
<td>Lymphodepletion (e.g., anti-CD20*)</td>
</tr>
<tr>
<td>Biologics (e.g., anti-tumor necrosis factor)</td>
<td>Antimetabolites (e.g., mycophenolate)</td>
<td>Solid organ transplant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AIDS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stem cell transplant</td>
</tr>
<tr>
<td></td>
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<td>Hematological malignancy</td>
</tr>
</tbody>
</table>

Sociodemographic factors and non-pharmaceutical interventions affect exposure

Original illustration by Dr. William Werbel, adapted for the COVID-19 Real-Time Learning Network

IDSA Immunocompromised Populations (https://www.idsociety.org/covid-19-real-time-learning-network/special-populations/immunocompromised-populations/)
# Summary of COVID-19 Preventative Agents & Therapeutics

## COVID-19 VACCINES

### Monoclonal Antibodies for PrEP
- **Evusheld** (tixagevimab + cilgavimab, AZ)

### None currently authorized for use in any US state or territory.

## Oral Antivirals
- **Paxlovid** (nirmatrelvir + ritonavir, Pfizer) - Preferred
- **Lagevrio** (molnupiravir, Merck) - Alternative

## Monoclonal Antibodies for Treatment
- **Bebtelovimab** (Lilly) - Alternative

## Exposed
- Per CDC Close Contact Criteria
  - Baseline health status, no infection
  - Not hospitalized, no limitations

## Mild to Moderate Symptoms
- Not hospitalized, with limitations
- Hosp. no act. medical problems

## Hospital Admission
- Hospitalized, not on oxygen
- Hospitalized, on oxygen
- Hosp. no act. medical problems

## ICU Admission
- Hospitalized, high flow oxygen/ non-invasive ventilation
- Hospitalized, mechanical ventilation/ ECMO

### Veklury® (remdesivir, Gilead) - Preferred

Please see [NIH Current Inpatient Therapies](https://www.covid19treatmentguidelines.nih.gov/therapies/)

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Tools to Assist in COVID-19 Outpatient Therapeutic Selection

As variant prevalence changes and new therapeutics become available, there are tools and resources available to assist in clinical decision-making for prescribers.

- **Clinical Decision Aid**: https://aspr.hhs.gov/COVID-19/Therapeutics/Documents/COVID-Therapeutics-Decision-Aid.pdf
- **NIH COVID-19 Treatment Guidelines Homepage**: https://www.covid19treatmentguidelines.nih.gov/therapies/
- **CDC COVID Data Tracker**: The CDC monitors and publishes variant information on the CDC Covid-19 Data Tracker (https://covid.cdc.gov/covid-data-tracker/#variant-proportions)
  - Information on variants of concern are updated in Section 15 of FDA fact sheets.
Emergency Use Authorization (EUA) of COVID-19 Therapeutics

• In certain types of emergencies, the FDA can issue an emergency use authorization (EUA), to provide more timely access to critical medical products (including medicines and tests) that may help during the emergency when there are no adequate, approved, and available alternative options.

• The EUA process is different than FDA approval, clearance, or licensing because the EUA standard may permit authorization based on significantly less data than would be required for approval, clearance, or licensing by the FDA. This enables the FDA to authorize the emergency use of medical products that meet the criteria within weeks rather than months to years. Since EUA products are not approved and, thus, do not have labeled indications, “off-label use” of them is not permitted.

• EUAs are in effect until the emergency declaration ends but can be revised or revoked as we evaluate the needs during the emergency and new data on the product’s safety and effectiveness, or as products meet the criteria to become approved, cleared, or licensed by the FDA.
Current Authorized or Approved COVID-19 Outpatient Therapeutics

- Each product under EUA has an FDA fact sheet for providers and one for patients and caregivers
- For any products with FDA-approved indications, the prescribing information is also included

- **Evusheld** (tixagevimab and cilgavimab)
  - Evusheld provider fact sheet: https://www.fda.gov/media/154701/download
  - Evusheld patient fact sheet: https://www.fda.gov/media/154702/download
  - Evusheld patient fact sheet (Spanish): https://www.fda.gov/media/155196/download

- **Paxlovid** (nirmatrelvir and ritonavir)
  - Paxlovid provider fact sheet: https://www.fda.gov/media/155050/download
  - Paxlovid patient fact sheet: https://www.fda.gov/media/155051/download
  - Paxlovid patient fact sheet (Spanish): https://www.fda.gov/media/155075/download

- **Lagevrio** (molnupiravir)
  - Lagevrio provider fact sheet: https://www.fda.gov/media/155054/download
  - Lagevrio patient fact sheet: https://www.fda.gov/media/155055/download
  - Lagevrio patient fact sheet (Spanish): N/A
Current Authorized or Approved COVID-19 Outpatient Therapeutics

• Each product under EUA has an FDA fact sheet for providers and one for patients and caregivers

• For any products with FDA-approved indications, the prescribing information is also included

  ▪ Bebtelovimab
    ➢ Bebtelovimab provider fact sheet: https://www.fda.gov/media/156152/download
    ➢ Bebtelovimab patient fact sheet: https://www.fda.gov/media/156153/download
    ➢ Bebtelovimab patient fact sheet (Spanish): https://www.fda.gov/media/156155/download

  ▪ Veklury (remdesivir)
    ➢ Veklury Prescribing Information: https://www.vekluryhcp.com/
Eligibility Criteria for Outpatient TREATMENT of Mild-to-Moderate COVID-19 Infection in High-Risk Patients

Mild to moderate COVID-19 cases early in infection, who are at high risk for progressing to severe COVID-19 and/or hospitalization;¹ with following criteria:

- Adult or pediatric patients 12 years of age and older weighing more than 40 kg
  - Exception: Lagevrio (molnupiravir) authorized in adult patients 18 years of age and older
- Confirmation via positive PCR or antigen test
- Treatment as soon as possible following positive viral test and within 5-7 days* of symptom onset
- Patient symptomatic but not yet progressed to require hospitalization or oxygen therapy (or increase from baseline chronic oxygen therapy) due to COVID-19

Monoclonal antibodies (mAbs) and Oral Antivirals (OAVs) given EUA for mild to moderate symptoms of COVID-19 are not authorized for use in patients:

- Who are hospitalized due to COVID-19, OR
- Who require oxygen therapy due to COVID-19, OR
- Who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity

¹CDC's Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals:

*Patient eligibility with respect to time since symptom onset varies across agents. See product fact sheets for product-specific durations.
PEDIATRIC Eligibility Criteria for Outpatient TREATMENT of Mild-to-Moderate COVID-19 Infection in High-Risk Patients

- Pediatric patients **28 Days of Age and Older and weighing 3 kg to less than 40 kg** with mild to moderate COVID-19 and at high risk for progression to severe disease
- Confirmation via **positive PCR or antigen test**
- Treatment **as soon as possible** after diagnosis of symptomatic COVID-19 and **within 7 days of symptom onset**

Only applies to Veklury (remdesivir)

**Veklury Prescribing Information**: [https://www.vekluryhcp.com/](https://www.vekluryhcp.com/)
Module 2: Product Information
Products for Pre-Exposure Prophylaxis (PrEP)
Evusheld (tixagevimab and cilgavimab) – AstraZeneca
Monoclonal Antibody for IM Injection

Evusheld Product Information
(https://www.evusheld.com)
Evusheld (tixagevimab and cilgavimab) Product Information

• FDA Fact Sheets
  ➢ Evusheld provider fact sheet: https://www.fda.gov/media/154701/download
  ➢ Evusheld patient fact sheet: https://www.fda.gov/media/154702/download
  ➢ Evusheld patient fact sheet (Spanish): https://www.fda.gov/media/155196/download

• Manufacturer’s Resources:
  ➢ Website for Healthcare Providers: https://www.evusheld.com/hcp
  ➢ Website for Patients: https://www.evusheld.com/patient

• Additional Resources:
  ➢ FDA MedWatch: https://www.accessdata.fda.gov/scripts/medwatch/index.cfm
  ➢ Safety Reporting: https://contactazmedical.astrazeneca.com/
  ➢ Module 4 Monoclonal Antibody Administration
Evusheld (tixagevimab and cilgavimab) Authorization

Evusheld (tixagevimab and cilgavimab) is indicated for PrEP of COVID-19 in adults and pediatric (12 years of age and older, weighing at least 40 kg):

Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2, **AND**

- Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination, **OR**

- For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).

For more information, [Fact Sheet for Health Care Providers for Evusheld (tixagevimab co-packaged with cilgavimab)](https://www.fda.gov/media/154701/download)
Evusheld (tixagevimab and cilgavimab): Limitations of Authorized Use

• Evusheld (tixagevimab and cilgavimab) is not authorized for use:
  ▪ For treatment of COVID-19.
  ▪ For post exposure prophylaxis (PEP) of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.

• PrEP with Evusheld (tixagevimab and cilgavimab) is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended. Individuals for whom COVID-19 vaccination is recommended, including individuals with moderate to severe immune compromise\(^1\) who may derive benefit from COVID-19 vaccination, should receive COVID-19 vaccination.

• In individuals who have received a COVID-19 vaccine, Evusheld (tixagevimab and cilgavimab) should be administered at least 2 weeks after last vaccination.

• Evusheld (tixagevimab and cilgavimab) may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which Evusheld belongs (i.e., antiinfectives).

\(^1\)CDC Clinical Considerations for COVID-19 Vaccines (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html)
Evusheld (tixagevimab and cilgavimab)

Dosage and Administration

- **Initial Dose:** 300 mg of tixagevimab and 300 mg of cilgavimab administered as two separate consecutive intramuscular injections.
  - Preferably one in each of the gluteal muscles, one after the other
- **Dosing for those who initially received 150 mg of tixagevimab and 150 mg of cilgavimab**
  - Initial dose ≤ 3 months ago, 150 mg of tixagevimab and 150 mg of cilgavimab ASAP
  - Initial dose > 3 months ago, 300 mg of tixagevimab and 300 mg of cilgavimab ASAP

Contraindications and Precautions

- History of severe hypersensitivity reactions, including anaphylaxis, to any component of Evusheld (tixagevimab and cilgavimab)
- Administer with caution to people with any coagulation disorder and at high risk for cardiovascular events
- Evusheld contains polysorbate 80, and there is a risk of cross-hypersensitivity with COVID-19 vaccines in susceptible individuals

For more information, [Fact Sheet for Healthcare Providers for Evusheld (tixagevimab and cilgavimab)](https://www.fda.gov/media/154701/download)
Evusheld (tixagevimab and cilgavimab):
Repeat Dosing

• The repeat dosage of EVUSHELD in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) is 300 mg of tixagevimab and 300 mg of cilgavimab administered every 6 months. Repeat dosing should be timed from the date of the most recent EVUSHELD dose. See table 1 on slide 22.

• Pharmacokinetic and pharmacodynamic modeling show that the currently circulating variants in the U.S. suggest in vivo activity against these variants may be retained at drug concentrations achieved following a single Evusheld initial dose of 300 mg tixagevimab and 300 mg cilgavimab for 6 months.

For more information, Fact Sheet for Healthcare Providers: Evusheld (tixagevimab and cilgavimab) (https://www.fda.gov/media/154701/download)
Evusheld (tixagevimab and cilgavimab): Dose Preparation

Each Evusheld carton contains two vials; one of each antibody. Each vial contains an overfill to allow the withdrawal of 150 mg (1.5 mL).

Table 1: Dosage of 300 mg of Tixagevimab and 300 mg of Cilgavimab

<table>
<thead>
<tr>
<th>Evusheld* (tixagevimab co-packaged with cilgavimab)</th>
<th>Antibody dose</th>
<th>Number of vials needed</th>
<th>Volume to withdraw from vial(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>tixagevimab</td>
<td>2 vials</td>
<td>3 mL</td>
</tr>
<tr>
<td></td>
<td>300 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cilgavimab</td>
<td>2 vials</td>
<td>3 mL</td>
</tr>
<tr>
<td></td>
<td>300 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 300 mg of tixagevimab and 300 mg of cilgavimab are to be administered as separate, consecutive intramuscular injections

Table 2: Dosage of 150 mg Tixagevimab and 150 mg Cilgavimab

<table>
<thead>
<tr>
<th>Evusheld* (tixagevimab co-packaged with cilgavimab)</th>
<th>Antibody dose</th>
<th>Number of vials needed</th>
<th>Volume to withdraw from vial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>tixagevimab</td>
<td>1 vial</td>
<td>1.5 mL</td>
</tr>
<tr>
<td></td>
<td>150 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cilgavimab</td>
<td>1 vial</td>
<td>1.5 mL</td>
</tr>
<tr>
<td></td>
<td>150 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 150 mg of tixagevimab and 150 mg of cilgavimab are to be administered as separate, consecutive intramuscular injections

For more information on Dose Preparation and Administration, see Section 2.3 of Fact Sheet for Healthcare Providers: Emergency Use Authorization For EVUSHELD™ (tixagevimab co-packaged with cilgavimab) (https://www.fda.gov/media/154701/download)
Products for Treatment of Mild-to-Moderate COVID-19
Paxlovid (nirmatrelvir and ritonavir) – Pfizer Oral Antiviral (Preferred)

Paxlovid Product Information: (https://www.paxlovid.com/)
Paxlovid (nirmatrelvir and ritonavir) Product Information

- **FDA Fact Sheets**
  - Paxlovid provider fact sheet: https://www.fda.gov/media/155050/download
  - Paxlovid patient fact sheet: https://www.fda.gov/media/155051/download
  - Paxlovid patient fact sheet (Spanish): https://www.fda.gov/media/155075/download

- **Manufacturer’s Resources:**

- **Additional Resources:**
  - Paxlovid Patient Eligibility Screening Checklist Tool for Prescribers: https://www.fda.gov/media/158165/download
  - Test to Treat Locator: https://aspr.hhs.gov/TestToTreat/Pages/default.aspx
  - Pfizer Safety Reporting: http://www.pfizersafetyreporting.com/
  - Module 5 Oral Therapeutics Administration
Paxlovid (nirmatrelvir and ritonavir) Authorization

- FDA has issued an EUA for the treatment of mild-to-moderate coronavirus disease (COVID-19) in adults (12 years of age and older weighing more than 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization and death, as soon as possible after diagnosis of COVID-19 and **within 5 days** of symptom onset.
- Paxlovid includes: nirmatrelvir (a SARS-CoV-2 main proteases inhibitor) and ritonavir (a CYP34A inhibitor)
- Limitations of authorized use:
  - Not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19
  - Paxlovid is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19
  - Not authorized for use longer than 5 consecutive days
- Paxlovid (nirmatrelvir and ritonavir) may be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which Paxlovid (nirmatrelvir and ritonavir) belongs (i.e., anti-infectives).

For more information, [Fact Sheet for Healthcare Providers for Paxlovid (nirmatrelvir and ritonavir)](https://www.fda.gov/media/155050/download)
Paxlovid (nirmatrelvir and ritonavir) - Pharmacist Prescribing Authorization

PAXLOVID may also be prescribed for an individual patient by a state-licensed pharmacist under the following conditions:

• Sufficient information is available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient, to assess renal and hepatic function; and

• Sufficient information is available, such as through access to health records, patient reporting of medical history, or consultation with a health care provider in an established provider-patient relationship with the individual patient, to obtain a comprehensive list of medications (prescribed and non-prescribed) that the patient is taking to assess for potential drug interaction.

For more information, Fact Sheet for Healthcare Providers for Paxlovid (nirmatrelvir and ritonavir) (https://www.fda.gov/media/155050/download)
The state-licensed pharmacist should refer an individual patient for clinical evaluation (e.g., telehealth, in-person visit) with a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs, if any of the following apply:

- Sufficient information is not available to assess renal and hepatic function.
- Sufficient information is not available to assess for a potential drug interaction.
- Modification of other medications is recommended due to a potential drug interaction.
- PAXLOVID is not an appropriate therapeutic option based on the authorized Fact Sheet for Healthcare Providers or due to potential drug interactions for which recommended monitoring would not be feasible.

For more information, Fact Sheet for Healthcare Providers for Paxlovid (nirmatrelvir and ritonavir) (https://www.fda.gov/media/155050/download)
Paxlovid (nirmatrelvir and ritonavir)

Dosage and Administration

- **eGFR > 60 mL/min**: 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) taken together twice daily for 5 days.

- **Dose reduction for moderate renal impairment eGFR > 30 mL/min to < 60 mL/min**: 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet) taken together twice daily for 5 days.

- **eGFR <30 mL/min**: currently not recommended

- **Severe hepatic impairment (Child-Pugh Class C)**: currently not recommended

Contraindications and Precautions

- History of clinically significant hypersensitivity reactions to the active ingredients or any other components.

- Co-administration with drugs highly dependent on CYP3A for clearance may result in life-threatening reactions\(^1\).

- Co-administration with potent CYP3A inducers may result in reduced nirmatrelvir plasma concentrations and potential loss of virologic response.

- The concomitant use of Paxlovid (nirmatrelvir and ritonavir) and certain other drugs may result in potentially significant drug interactions.

- Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir.

- Paxlovid (nirmatrelvir and ritonavir) use may lead to a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.

\(^1\)Liverpool Covid-19 interaction checker: (https://covid19-druginteractions.org/)

For more information, Fact Sheet for Healthcare Providers for Paxlovid (nirmatrelvir and ritonavir) (https://www.fda.gov/media/155050/download)
Paxlovid (nirmatrelvir and ritonavir) Patient Eligibility Screening Checklist Tool for Prescribers

**Medical History**

- Positive SARS-CoV-2 test
- Age ≥ 12 years of age and weighing at least 40 kg
- Has one or more risk factors for progression to severe COVID-19
- Symptoms consistent with mild to moderate COVID-19
- Symptom onset within 5 days
- Not requiring hospitalization due to severe or critical COVID-19 at treatment initiation
- No known or suspected severe renal impairment (eGFR < 30 mL/min)
  - Note that a dose reduction is required for patients with moderate renal impairment (eGFR ≥30–<60 mL/min); see the Fact Sheet for Healthcare Providers.
  - Prescriber may rely on patient history and access to the patient's health records to make an assessment regarding the likelihood of renal impairment. Providers may consider ordering a serum creatinine or calculating the estimated glomerular filtration rate (eGFR) for certain patients after assessment on a case-by-case basis based on history or exam.
- No known or suspected severe hepatic impairment
- No history of clinically significant hypersensitivity reactions to the active ingredients (nirmatrelvir or ritonavir) or other components of the product

See table in Paxlovid Patient Eligibility Screening Checklist Tool for Prescribers [https://www.fda.gov/media/158165/download](https://www.fda.gov/media/158165/download)
Concomitant Medications

- **Assess patient’s home medication list for drug-drug interactions**
- See table in Paxlovid Patient Eligibility Screening Checklist Tool for Prescribers https://www.fda.gov/media/158165/download
- HMG-CoA reductase inhibitors (statins)
  - Patient is taking lovastatin or simvastatin, which are contraindicated with PAXLOVID coadministration: The statin can be held 12 hours prior to the first dose of PAXLOVID treatment, held during the 5 days of treatment, and restarted 5 days after completing PAXLOVID.
  - Patient is taking atorvastatin or rosuvastatin: Temporary discontinuation of atorvastatin and rosuvastatin during treatment with PAXLOVID should be considered depending on statin dose. Atorvastatin and rosuvastatin do not need to be held prior to or after completing PAXLOVID.
- Hormonal contraceptives containing ethinyl estradiol: Patient is taking a hormonal contraceptive containing ethinyl estradiol: The need for an additional non-hormonal method of contraception during the 5 days of PAXLOVID treatment and until one menstrual cycle after stopping PAXLOVID should be recommended.
- Medications for HIV-1 Treatment: Patient is taking medications for the treatment of HIV-1 infection: With the exception of maraviroc3, HIV antiretroviral medications can be co-administered with PAXLOVID without dose adjustment, but arranging follow-up by the HIV care provider to monitor for side effects is recommended

Other Drugs with Established and Other Potentially Significant Drug Interactions with PAXLOVID

- See table in Paxlovid Patient Eligibility Screening Checklist Tool for Prescribers https://www.fda.gov/media/158165/download

*Prescriber is encouraged to include a note to the pharmacist in the prescription stating:

Please fill prescription by [insert date]. This prescription fill by date is within 5 days from symptom onset and complies with the patient eligibility criteria under the EUA.
Paxlovid (nirmatrelvir and ritonavir) Patient Eligibility Screening Checklist Tool for Prescribers (Table)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Class</th>
<th>Interaction Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>Antihyperuric</td>
<td>XXX</td>
</tr>
<tr>
<td>Anagrelide</td>
<td>Antithrombotic</td>
<td>XXX</td>
</tr>
<tr>
<td>Amlodipine</td>
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<td>Dronedarone</td>
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</table>

See table in Paxlovid Patient Eligibility Screening Checklist Tool for Prescribers
https://www.fda.gov/media/158165/download
Additional Paxlovid Prescribing Resources

2. FDA PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers: (https://www.fda.gov/media/158165/download)
Paxlovid (nirmatrelvir and ritonavir) 
Formulation and Packaging

The FDA updated the Paxlovid EUA to authorize an additional dose pack presentation of Paxlovid with appropriate dosing for patients within the scope of this authorization with moderate renal impairment. (https://www.fda.gov/media/155050/download)

**Minimum Order Quantity: 20**

**Standard Dose**

300 mg nirmatrelvir; 100 mg ritonavir: Each carton contains 30 tablets divided in 5 daily dose blister cards. Each blister card contains 4 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each). Nirmatrelvir tablets and ritonavir tablets are supplied in separate blister cavities within the same child-resistant blister card.

**Minimum Order Quantity: 5**

**Renal Dose**

150 mg nirmatrelvir; 100 mg ritonavir: Each carton contains 20 tablets divided in 5 daily dose blister cards. Each blister card contains 2 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each). Nirmatrelvir tablets and ritonavir tablets are supplied in separate blister cavities within the same child-resistant blister card.

ASPR's COVID19 Therapeutics website (https://aspr.hhs.gov/COVID-19/Pages/default.aspx)
New and Notable: COVID-19 Therapeutics Announcements (https://aspr.hhs.gov/COVID-19/Therapeutics/Pages/default.aspx)
Paxlovid (nirmatrelvir and ritonavir)
Renal Adjustment Sticker Application Instructions for Pharmacists for Standard Dose Pack

Viral RNA Rebound

• Post-treatment increases in SARS-CoV-2 RNA levels (i.e., viral RNA rebound) in nasopharyngeal samples were observed on Day 10 and/or Day 14 in a subset of Paxlovid and placebo recipients, irrespective of COVID-19 symptoms. The frequency of detection of post-treatment viral RNA rebound varied according to analysis parameters but was generally similar among Paxlovid and placebo recipients, regardless of the rebound definition used. A similar or smaller percentage of placebo recipients compared to Paxlovid recipients had nasopharyngeal viral RNA results < LLOQ at all study timepoints in both the treatment and post-treatment periods.

• Post-treatment viral RNA rebound was not associated with the primary clinical outcome of COVID-19-related hospitalization or death from any cause through Day 28 following the single 5-day course of Paxlovid treatment. Post-treatment viral RNA rebound also was not associated with drug resistance as measured by Mpro sequencing. The clinical relevance or exact incidence of post-treatment increases in viral RNA following Paxlovid or placebo treatment is unknown at this time.

• Viral RNA rebound is not specific to Paxlovid and has been demonstrated in Lagevrio.

See: Microbiology (12.4): addition of viral RNA rebound" ***Not exclusive to Paxlovid***: (https://www.fda.gov/media/155050/download)
Lagevrio (molnupiravir) – Merck *Oral Antiviral (Alternative)*

Lagevrio (molnupiravir) Product Information
https://www.molnupiravir-us.com/
Lagevrio (molnupiravir) Product Information

- FDA Fact Sheets
  - Lagevrio (molnupiravir) provider fact sheet: https://www.fda.gov/media/155054/download
  - Lagevrio (molnupiravir) patient fact sheet: https://www.fda.gov/media/155055/download
  - Lagevrio (molnupiravir) patient fact sheet (Spanish): N/A

- Manufacturer’s Resources:
  - Website for Healthcare Providers: https://www.molnupiravir-us.com/hcp/
  - Website for Patients: https://www.molnupiravir-us.com/patients/
  - Report a Pregnancy Exposure: https://pregnancyreporting.msd.com/

- Additional Resources:
  - Test to Treat Locator: https://aspr.hhs.gov/TestToTreat/Pages/default.aspx
  - Safety Reporting Email: dpoc.usa@msd.com
  - Module 5 Oral Therapeutics Administration
Lagevrio (molnupiravir) Authorization

- Lagevrio (molnupiravir) has been authorized by FDA under an EUA, for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing who are at high-risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 outpatient treatment options approved or authorized by FDA are not accessible or clinically appropriate.

- Not authorized for:
  - Patients less than 18 years of age
  - Initiation of treatment in patients requiring hospitalization due to COVID-19
  - Use longer than 5 consecutive days

- Lagevrio (molnupiravir) may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which Lagevrio (molnupiravir) belongs (i.e., anti-infectives).

For more information, [Fact Sheet for Healthcare Providers for Lagevrio (molnupiravir)](https://www.fda.gov/media/155054/download)
Lagevrio (molnupiravir)

Dosage and Administration

• 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food.

• Take Lagevrio (molnupiravir) as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset.

• Not authorized for use for longer than 5 consecutive days.

Contraindications and Precautions

• No contraindications have been identified based on the limited available data on the emergency use of Lagevrio (molnupiravir) authorized under this EUA.

• Not recommended for use during pregnancy and not authorized for use in patients under 18 years of age.

• Hypersensitivity reactions, including anaphylaxis have been reported with Lagevrio (molnupiravir). If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue Lagevrio (molnupiravir).

For more information, Fact Sheet for Healthcare Providers for Lagevrio (molnupiravir) (https://www.fda.gov/media/155054/download)
Lagevrio (molnupiravir) Provider Checklist

- Positive SARS-CoV-2 test
- Age ≥18 years
- Alternate COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate
- High-risk criteria met
- Symptoms consistent with mild-moderate COVID-19
- Symptom onset with 5 days*
- Not hospitalized due to COVID-19
- Assessment pregnancy and breastfeeding status (if applicable)
- Provide appropriate counseling
  - Females of childbearing potential treated: should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of Lagevrio (molnupiravir)
  - Breastfeeding is not recommended for the duration of treatment and for 4 days after the last dose of Lagevrio (molnupiravir)
  - Males of reproductive potential treated: if sexually active with females of childbearing potential, should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose of Lagevrio (molnupiravir)

*Prescriber is encouraged to include a note to the pharmacist in the prescription stating: Please fill prescription by [insert date]. This prescription fill by date is within 5 days from symptom onset and complies with the patient eligibility criteria under the EUA.

For more information, Prescriber Checklist for Molnupiravir (https://www.fda.gov/media/155118/download)
Lagevrio (molnupiravir) Prescriber Requirements

All Patients
1. Provide electronic or hard copy of patient fact sheet
2. Document* that patient has received an electronic or hard copy of the patient fact sheet
3. Review the information contained within the patient factsheet with the patient and counsel patient on the known and potential benefits and risks of Lagevrio (molnupiravir)
4. Advise patients on need for contraception use as appropriate
   • Females of childbearing potential treated: should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of Lagevrio (molnupiravir)
   • Breastfeeding is not recommended for the duration of treatment and for 4 days after the last dose of Lagevrio (molnupiravir)
   • Males of reproductive potential treated: if sexually active with females of childbearing potential, should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose of Lagevrio (molnupiravir)
5. The prescribing healthcare provider and/or the provider’s designee must report all medication errors and serious adverse events potentially related to Lagevrio (molnupiravir) within 7 calendar days from the healthcare provider’s awareness of the event
   • Complete and submit the report online: www.fda.gov/medwatch/report.htm

*How and where documentation occurs is at the discretion of the prescribing health care provider and their clinical site.
Individuals of Childbearing Potential

1. Assess whether pregnant or not
   • Report of last menstrual period in an individual who has regular menstrual cycles, uses a reliable method of contraception correctly and consistently or has had a negative pregnancy test
   • Negative pregnancy test (recommended but not required if other criteria are not met)

2. If pregnant:
   • Counsel the patient regarding the known and potential benefits and potential risks of Lagevrio (molnupiravir) use during pregnancy
   • Document* that the patient is aware of the known and potential benefits and potential risks of Lagevrio (molnupiravir) use during pregnancy
   • Make the individual aware of the pregnancy surveillance program
   • If the pregnant individual agrees to participate in the pregnancy surveillance program and allows the prescribing healthcare provider to disclose patient specific information to Merck, the prescribing healthcare provider must provide the patient's name and contact information to Merck (at 1-877-888-4231 or pregnancyreporting.msd.com)

3. If not pregnant:
   • Make the individual and their partner aware of the pregnancy surveillance program and encourage them to participate should they become pregnant
   • Review contraception requirements per Lagevrio Providers Fact Sheet (https://www.fda.gov/media/155054/download)

*How and where documentation occurs is at the discretion of the prescribing health care provider and their clinical site.
Veklury (remdesivir) – GileadAntiviral for IV Infusion (Preferred)

Veklury Product Information
https://www.vekluryhcp.com/
Veklury (remdesivir) Product Information

• Prescribing Information & FDA Fact Sheets

• Manufacturer’s Resources:
  - Website for Healthcare Providers: https://www.vekluryhcp.com/
  - Website for Patients: https://www.veklury.com/

• Additional Resources:
  - Safety Reporting Email: Safety_fc@gilead.com
Veklury (remdesivir) – Outpatient Use

• FDA **approved** expanded use of Veklury (remdesivir) to certain **non-hospitalized** adults and pediatric patients for treatment of mild-to-moderate COVID-19 disease (Jan 21, 2022), including:
  - Adults and pediatric patients 28 days of age and older and weighing at least 3 kg with positive results of direct SARS-CoV-2 viral testing, **AND**
  - Who are not hospitalized and have mild-to-moderate COVID-19 and are at high risk for progression to severe COVID-19, including hospitalization or death

• The treatment course of Veklury (remdesivir) should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made and **within 7 days** of symptom onset. The recommended total duration of treatment for non-hospitalized patients is 3 days.

Veklury (remdesivir)

Dosage and Administration

- **Dosage:**
  - For adults and pediatric patients 12 years of age and older weighing more than 40 kg: **200 mg** on Day 1, followed by once-daily maintenance doses of **100 mg** from Day 2 administered only via intravenous infusion over 30 to 120 minutes
  
  - For pediatric patients 28 days of age and older and weighing 3 kg to less than 40 kg: **5 mg/kg** on Day 1 followed by **2.5 mg/kg** once daily from Day 2

- **Dosage Forms:**
  - For injection: **100 mg** of remdesivir as a lyophilized powder, in a single-dose vial
  
  - Injection: **100 mg/20 mL (5 mg/mL)** remdesivir, in a single-dose vial

Contraindications and Precautions

- History of clinically significant hypersensitivity reactions to Veklury or any components of the product
  
  - Hypersensitivity including infusion-related and anaphylactic reactions
  
  - Increased risk of transaminase elevations
  
  - Risk of reduced antiviral activity when coadministered with chloroquine phosphate or hydroxychloroquine sulfate

- Monitor patients during infusion

- **Observe patients for at least one hour after infusion is complete for signs and symptoms of hypersensitivity as clinically appropriate.**

Veklury (remdesivir) (continued)
Pediatric Dosing and Administration:

<table>
<thead>
<tr>
<th>Body weight</th>
<th>Recommended dosage form</th>
<th>Loading dose (on Day 1)</th>
<th>Maintenance dose (from Day 2)</th>
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</thead>
<tbody>
<tr>
<td>3 kg to less than 40 kg</td>
<td>Veklury for injection, lyophilized powder Only</td>
<td>5 mg/kg</td>
<td>2.5 mg/kg</td>
</tr>
</tbody>
</table>

- Lyophilized powder: **100 mg** of Veklury (remdesivir) reconstituted with 19 mL of Sterile Water for Injection. The only approved dosage form of Veklury for pediatric patients weighing 3 kg to less than 40 kg is Veklury for injection (supplied as 100 mg lyophilized powder in vial).

- Further dilute to a concentration of 1.25 mg/mL using 0.9% sodium chloride
  - Small 0.9% sodium chloride infusion bags (e.g., 25, 50, or 100 mL) or an appropriately sized syringe should be used for pediatric dosing.
  - This product is not recommended in patients with eGFR less than 30 mL/min

Veklury (remdesivir) (continued)
Recommended Rate of Infusion-Diluted Veklury for Injection Lyophilized Powder for Pediatric Patients Weighing 3 kg to Less than 40 kg

<table>
<thead>
<tr>
<th>Infusion volume</th>
<th>Infusion time(^1)</th>
<th>Rate of infusion</th>
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</thead>
<tbody>
<tr>
<td>100 L</td>
<td>30 min</td>
<td>3.33 mL/min</td>
</tr>
<tr>
<td></td>
<td>60 min</td>
<td>1.67 mL/min</td>
</tr>
<tr>
<td></td>
<td>120 min</td>
<td>0.83 mL/min</td>
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<tr>
<td>50 mL</td>
<td>30 min</td>
<td>1.67 mL/min</td>
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<td>60 min</td>
<td>0.83 mL/min</td>
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<tr>
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<td>120 min</td>
<td>0.42 mL/min</td>
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<td>25 mL</td>
<td>30 min</td>
<td>0.83 mL/min</td>
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<td>60 min</td>
<td>0.42 mL/min</td>
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<tr>
<td></td>
<td>120 min</td>
<td>0.06 mL/min</td>
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</table>

\(^1\) see section 2.6 of Veklury (remdesivir) Prescribing Information (https://www.gilead.com/-/media/files/pdfs/medicines/COVID-19/veklury/veklury_pi.pdf)
Bebtelovimab – Eli Lilly
Monoclonal Antibody for IV Injection - IV Push (Alternative)

bebtelovimab Product Information
http://www.lillyantibody.com/bebtelovimab
Bebtelovimab Product Information

• FDA Fact Sheets
  - Bebtelovimab provider fact sheet: https://www.fda.gov/media/156152/download
  - Bebtelovimab patient fact sheet: https://www.fda.gov/media/156153/download
  - Bebtelovimab patient fact sheet (Spanish): https://www.fda.gov/media/156155/download

• Manufacturer’s Resources:
  - Website for Healthcare Providers: https://www.covid19.lilly.com/bebtelovimab/hcp
  - Website for Patients: https://www.covid19.lilly.com/bebtelovimab

• Additional Resources:
  - Safety Reporting Email: mailindata_gsmtindy@lilly.com
  - Module 4 Monoclonal Antibody Administration
Bebtelovimab Authorization

- FDA has issued an EUA to permit the emergency use of bebtelovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg):
  - With positive results of direct SARS-CoV-2 viral testing, **AND**
  - Who are at high risk for progression to severe COVID-19, including hospitalization or death, **AND**
  - For whom alternative COVID-19 treatment options are not clinically appropriate or accessible.

  *Per EUA: FDA does not consider Veklury® (remdesivir) to be an adequate alternative to bebtelovimab for this authorized use because it may not be feasible or practical for certain patients (e.g., it requires a 3-day treatment duration)*

  *Per NIH Guidelines: The Panel recommends using bebtelovimab as an alternative therapy **ONLY** when ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir are not available, feasible to use, or clinically appropriate (CIII). Treatment should be initiated as soon as possible and within 7 days of symptom onset. See [Therapeutic Management of Nonhospitalized Adults With COVID-19](https://www.fda.gov/media/156152/download) for further guidance.*

- Bebtelovimab is not authorized for use in patients:
  - Who are hospitalized due to COVID-19, **OR**
  - Who require oxygen therapy due to COVID-19, **OR**
  - Who require an increase in baseline oxygen flow rate due to COVID-19 (in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity).

For more information, [Fact Sheet for Healthcare Providers for Bebtelovimab](https://www.fda.gov/media/156152/download).
Bebtelovimab Dosage and Administration

- For adults and pediatric patients (12 years of age and older weighing at least 40 kg): **175 mg** administered as a single IV injection (i.e., IV push) over at least 30 seconds.
- **Bebtelovimab** injection should be prepared by a qualified healthcare professional using aseptic technique.
- Patients should be clinically monitored during and for one hour after bebtelovimab administration.
- **Bebtelovimab** should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing, and within 7 days of symptom onset.

For more information, [Fact Sheet for Healthcare Providers for Bebtelovimab](https://www.fda.gov/media/156152/download)
Bebtelovimab Preparation

• Remove bebtelovimab vial from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation.
  
  ▪ **Do not expose to direct heat. Do not shake vial. Inspect the vial.**

• Withdraw 2 mL from the vial into the disposable syringe.

• Discard any product remaining in the vial.

• This product is preservative-free and therefore, should be administered immediately.
  
  ▪ If immediate administration is not possible, store the syringe for up to 24 hours at refrigerated temperature (2 °C to 8 °C [36 °F to 46 °F]) and up to 7 hours at room temperature (20 °C to 25 °C [68 °F to 77 °F]).
  
  ▪ If refrigerated, allow the prepared syringe to equilibrate to room temperature for approximately 20 minutes prior to administration.

• If used, attach and prime the syringe extension set.

• Administer the entire contents of the syringe via IV injection over at least 30 seconds.

• After the entire contents of the syringe have been administered, **flush the extension set** with 0.9% sodium chloride to ensure delivery of the required dose.
Module 3: Reimbursement
CMS and HRSA Resources

CMS Resources:

- Oral Antiviral NDC Numbers:
  - Renal Paxlovid 0069-1101-20
  - Lagevrio (molnupiravir): 0006-5055-06, 0006-5055-07

Continue to check CMS website for most up to date information: [www.CMS.gov](http://www.CMS.gov)

HRSA Resources:

- As of March 22, 2022, The Uninsured Program stopped accepting claims for testing and treatment due to lack of sufficient funds. (https://www.hrsa.gov/CovidUninsuredClaim)
CMS: Coverage of Monoclonal Antibody Products to Treat COVID-19

Expected Payment to Providers: Key Facts

- Medicare payment for monoclonal antibody products to treat COVID-19 is similar across sites of care, with some small differences.
- Medicare pays for the administration of monoclonal antibody products to treat COVID-19. For example, Medicare will pay a national average of approximately $450 for the administration of certain monoclonal antibody products. Home infusion is reimbursed at a higher rate.
- CMS will exercise enforcement discretion to allow Medicare-enrolled immunizers working within their scope of practice and subject to applicable state law to bill directly and receive direct reimbursement from the Medicare program for administering monoclonal antibody treatments to Medicare Part A Skilled Nursing Facility residents.
- Medicare will pay the provider for these monoclonal antibody products when they are purchased by the provider. Medicare won’t pay if the product is given to the provider for free by, for example, a government entity.
- When purchased by the provider, Medicare payment is typically at reasonable cost or at 95% of the Average Wholesale Price (an amount determined by the manufacturer). These payment amounts vary depending on which type of provider is supplying the product. Original Medicare will pay for these products for beneficiaries enrolled in Medicare Advantage.
- For more specific information about Medicare payments to providers for these monoclonal antibody products, please see these Frequently Asked Questions.

CMS: Coverage of Oral Antiviral Therapies to Treat COVID-19

<table>
<thead>
<tr>
<th>Site of Care1</th>
<th>Payable by Medicare</th>
<th>Expected Patient Cost-Sharing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient Hospital</td>
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<td>No patient cost-sharing</td>
</tr>
<tr>
<td>Outpatient Hospital or “Hospital without Walls”2</td>
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<td>No patient cost-sharing</td>
</tr>
<tr>
<td>Outpatient Physician Office</td>
<td>✔️</td>
<td>No patient cost-sharing3</td>
</tr>
<tr>
<td>Nursing Home</td>
<td>✔️</td>
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</tr>
<tr>
<td>Pharmacy</td>
<td>✔️</td>
<td>No patient cost-sharing</td>
</tr>
</tbody>
</table>

1 Services must be furnished within the scope of the product’s FDA authorization or approval and within the provider’s scope of practice.

2 Under the Hospital Without Walls initiative, hospitals can provide hospital services in other healthcare facilities and sites that would not otherwise be considered to be part of a healthcare facility; or can set up temporary expansion sites to help address the urgent need to increase capacity to care for patients.

3 Cost-sharing may apply to Medicare beneficiaries when they receive care from a provider that doesn’t participate in Medicare.

**Expected Payment to Providers: Key Facts**

- CMS will provide a list of pharmacies that have provider agreements with the USG to dispense the drug in compliance with the terms and conditions of authorization. CMS will provide a list of these pharmacies, including National Provider Identifier (NPI), on the Health Plan Management Site as soon as it is available.

- Pay dispensing fees: While certain USG-procured oral antiviral drug(s) will be made available at no cost to pharmacies, the procurement does not include payment of a dispensing fee to pharmacies. CMS encourages Part D sponsors to pay a dispensing fee to pharmacies that submit claims for these drugs. No ingredient cost can be paid on these claims.

- Part D sponsors should not charge enrollee cost sharing on dispensing fees paid to the pharmacies.

- Sponsors should consult NCPDP Emergency Preparedness Guidance for “Billing for Reimbursement of a Free Product (No associated cost) with No Administration Fee” as they prepare to implement these changes.

CMS Code for Outpatient Veklury (remdesivir)

- CMS created **HCPCS code J0248** for the Veklury (remdesivir) antiviral medication when administered in outpatient setting

- Code available for use by all payers

- Effective dates of service on or after December 23, 2021:
  - Long descriptor: Injection, remdesivir, 1 mg
  - Short descriptor: Inj, remdesivir, 1 mg

- Medicare Administrative Contractors (MACs) determine Medicare coverage when no national coverage determination, including when providers use FDA-approved drugs for indications other than what is on approved label

- MACs will determine Medicare coverage for HCPCS code J0248 for Veklury (remdesivir) administered in outpatient setting

- See [CMS Website](https://www.cms.gov/monoclonal) for additional information (https://www.cms.gov/monoclonal)
Module 4:
Monoclonal Antibody Administration
Monoclonal Antibody Administration Can Occur Across a Wide Variety of Models

- **Hospital**
  - Hospital-based infusion centers
  - Emergency departments
  - Urgent care/Obs units/Fast track areas
  - Converted space within hospital for COVID infusion
  - Alternate care sites

- **Ambulatory center**
  - Infusion centers
  - Urgent care clinics
  - Dialysis centers
  - Alternate care sites

- **Nursing homes**
  - Skilled nursing facilities
  - Long-term care facilities

- **Mobile sites**
  - Bus/trailer
  - Other mobile sites

- **Home**
  - At patient's home
Pathway to Monoclonals:
Patient with Confirmed COVID-19 Infection

- Treatment likely most beneficial to patients if given **early in symptom progression**
- EUA requires administration of **treatment as soon as possible after** confirmed positive test result and within **7 days of symptom onset**
- Strong **partnership and communication** between patients and HCP to get right treatment to right patients at right time
- Fast testing turnaround needed, to efficiently **identify positive tests** and **schedule for treatment**

**Example of timeline which would fulfill EUA requirements**

<table>
<thead>
<tr>
<th>Event</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of symptoms</td>
<td></td>
</tr>
<tr>
<td>Clinical visit and diagnostic test</td>
<td>≤ 3 days post symptom onset</td>
</tr>
<tr>
<td>Confirmed positive test</td>
<td>≤ 24 hours post diagnostic test</td>
</tr>
<tr>
<td>Treatment</td>
<td>ASAP post positive test result</td>
</tr>
</tbody>
</table>

- **Treatment required within 7 days of symptom onset**
- **Testing sites should recommend COVID+ patients that are high risk confer with their HCP on potential suitability for Tx**

**Early administration of treatment needs fast testing turn-around and patient scheduling**

**Planning required for "Test to Treat" or "Test and Refer" models**

Please reference EUA factsheet for specific treatment guidelines including recommended treatment window
## Patient Flow for Outpatient mAbs Product

**Scenario 1: Confirmed positive patient referred for treatment**

<table>
<thead>
<tr>
<th>Pre-treatment</th>
<th>Treatment</th>
<th>Post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirm documentation of COVID-19 infection via either</strong></td>
<td><strong>Pre-book time for administration space and follow clear protocol for coming onsite</strong></td>
<td><strong>Discharge patient immediately following monitoring completion</strong></td>
</tr>
<tr>
<td>• Participant-provided lab report</td>
<td>• Ensure operationally ready to receive and treat the patient</td>
<td>• Follow clear protocol to minimize risk of exposure to others</td>
</tr>
<tr>
<td>• Medical record lab report</td>
<td>• Use CDC recommended practices to minimize exposure to others</td>
<td><strong>Post-treatment care encouraged to be via telemedicine as possible</strong></td>
</tr>
<tr>
<td>• Direct communication from a provider or laboratory</td>
<td><strong>Provide treatment to patient</strong></td>
<td>• Normal follow-up care, no special data tracking requirements</td>
</tr>
<tr>
<td><strong>Discuss treatment with patient</strong></td>
<td>• Infusion duration up to ~1 hr(^1) with an additional 1 hr of observation post infusion (checks during infusion and observation)</td>
<td><strong>Post-treatment steps should be completed via telemedicine as possible (~30 mins)</strong></td>
</tr>
<tr>
<td>• Ensure patient meets treatment requirements and understands risks</td>
<td>• Infusion pumps or gravity-based infusion acceptable</td>
<td><strong>Pre-treatment steps should be completed via telemedicine as possible (~30 mins)</strong></td>
</tr>
<tr>
<td><strong>Schedule the patient to come in for treatment ASAP</strong></td>
<td><strong>Ensure preparation for administration reactions as unlikely but possible side effect</strong></td>
<td><strong>Pre-treatment steps should be completed via telemedicine as possible (~30 mins)</strong></td>
</tr>
<tr>
<td>• Provide guidance on site visit protocols to patients</td>
<td>• Infusion rate may be reduced based on patient circumstances</td>
<td><strong>Pre-treatment steps should be completed via telemedicine as possible (~30 mins)</strong></td>
</tr>
<tr>
<td>• Provide patient education on what to expect with administration</td>
<td>• Ensure emergency action plan in place; ability to activate EMS if necessary, a requirement for administration under EUA</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Contingent on product dilution, reference EUA fact sheet for dilution and infusion timing
Patient Flow for Outpatient mAbs Product

Scenario 2 and 3: Patient arrives for testing at site with unknown diagnosis

Same process as Scenario 1

### Pre-treatment

Direct patient to typical testing process for site (onsite or offsite)
- Quick response testing needed for early diagnosis to enable early treatment

Assuming patient discharged to await test results, once patient confirmed positive outreach on treatment (~30 mins):
- Discuss treatment with patient
  - Ensure patient meets treatment requirements and understands risks
  - Provide guidance on administration and site visit protocols to patients
- Schedule the patient to come in for treatment ASAP
- Pre-treatment discussion and scheduling should be via telemedicine as possible

In case of point-of-care rapid testing, consider same-day administration needs
- Isolated location for patient to wait
  Availability of treatment space and staff

### Treatment

Pre-book time for administration space and follow clear protocol for coming onsite
- Ensure operationally ready to receive and treat the patient
- Use CDC recommended practices to minimize exposure to others

Provide treatment to patient
- Infusion duration up to ~1 hr\(^1\) with an additional 1 hr of observation post infusion (checks during infusion and observation)
- Infusion pumps or gravity-based infusion acceptable

Ensure preparation for administration reactions as unlikely but possible side effect
- Infusion rate may be reduced based on patient circumstances
- Ensure emergency action plan in place; ability to activate EMS if necessary, a requirement for administration under EUA

### Post-treatment

Discharge patient immediately following monitoring completion
- Follow clear protocol to minimize risk of exposure to others

Post-treatment care encouraged to be via telemedicine as possible
- Normal follow-up care, no special data tracking requirements

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\(^1\)Contingent on product dilution, reference EUA fact sheet for dilution and infusion timing
Sample Staffing Models for Antibody Administration

Examples of staff plans *(recommended positions may vary depending on the State’s scope of practice for Paramedics as it related to Subcutaneous and or Intravenous administration of medications or mAbs)*

- 8-10 bed mAb infusion/observation site
  - 1 physician / advanced practitioner (present or available via telemedicine)
  - 2 Nurses
  - 1 Nurse or Paramedic
  - 2 Paramedics
  - 1 flex position – administrative/ logistics/ runner

- Single station or mobile visit Subcutaneous administration site
  - 1 physician / advanced practitioner (present or available via telemedicine)
  - 1 Nurse / Paramedic per single mobile visit or single station

Average patient (door to door) visit can range from 80-120 minutes

**COVID-19 Monoclonal Antibody Therapeutics Calculator for Infusion Sites** (https://www.phe.gov/emergency/mAbs-calculator/Pages/default.aspx)
Site Preparation for mAb Administration

- Collect administration site location(s), address, and points of contact
  - For mobile or deployed teams, identify the point of contact at the administration site and make contact
  - Site will need dedicated space for isolation of COVID-19 patients¹
  - Rededication of existing clinical space is permitted under the CMS Hospital Without Walls Initiative
- Ensure a patient scheduling and referral process is in place
- Identify and understand which therapeutics will be administered
- Determine who is responsible for ordering the monoclonal antibody administration
  - Referring provider
  - On-site or telemedicine provider
  - Standing order
- Brief administration team with site objectives
- Team training
  - Site workflow
  - Monoclonal administration
  - Managing adverse reactions with rescue medications on site as applicable

mAbs Preparation

Administration preparation process:
• Prepare sterile infusions in a manner consistent with local laws, regulations, guidelines and policies
• Obtain new vial(s) and/or IV bags if the drug product contains any visible particulate matter

Needs for space to prepare mAb drug:
• Dedicated preparation area with sufficient capacity onsite or nearby

Acceptable equipment for mAb drug storage:
• Refrigerated storage (2-8 °C)
• Temperature control mechanism including temperature monitoring process

Please see EUA manufacturer fact sheet for drug-specific requirements

*Note: product can be prepared for infusion and subcutaneous administration bedside by any qualified medical professional*
Post-mAbs Administration Observation

- Per EUA, “Clinically monitor patients during dose administration and observe patients for at least 1 hour after intravenous infusion or subcutaneous dosing is complete”
- Provide education on follow-up, required isolation per CDC guidelines after COVID-19 exposure or diagnosis, red flags for seeking emergency care
- Respond to severe adverse events/ anaphylaxis
- “Discharge” patient after one-hour post-administration observation if stable and without symptoms of severe adverse reaction, otherwise consider further observation or emergency department evaluation if clinical concern
- Report any severe adverse events as required by the FDA through the process outlined in the EUA
Managing Adverse Reactions to mAbs

- **Monoclonal antibodies may only be administered** in settings in which health care providers have immediate access to medications (e.g., epinephrine) to treat a severe infusion or hypersensitivity reactions, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

- Early identification of anaphylaxis. Symptoms may include:
  - Respiratory: throat tightness, stridor, hoarseness, wheezing, respiratory distress, coughing, trouble swallowing/drooling, nasal congestion/drainage, sneezing
  - Gastrointestinal: nausea, vomiting, diarrhea, abdominal pain, cramps
  - Cardiovascular: dizziness, fainting, tachycardia, hypotension, cyanosis, pallor, flushing
  - Skin/mucosal: hives, erythema, itching, swelling of eyes, lips, tongue, mouth, face, or extremities
  - Neurologic: agitation, convulsions, altered mental status, sense of impending doom
  - Other: sudden increase in secretions, urinary incontinence
Managing Adverse Reactions to mAbs: Medications and Equipment

- **Should be available** at all sites:
  - Epinephrine (e.g., prefilled syringe or autoinjector)
  - H1 antihistamine (e.g., diphenhydramine, cetirizine)
  - Blood pressure monitor

- **If feasible**, include at sites (not required)
  - Oxygen
  - Bronchodilator (e.g., albuterol)
  - H2 antihistamine (e.g., famotidine, cimetidine)
  - Intravenous fluids
  - Intubation kit
  - Adult-sized pocket mask with one-way valve (CPR mask)

Adapted from [CDC Interim Considerations](https://www.cdc.gov/vaccines/covid-19/downloads/IntermConsid-Anaphylaxis-covid19-vaccine-sites.pdf): Preparing for the potential management of anaphylaxis at COVID-19 vaccination sites
mAbs Administration Site Record-Keeping and Adverse Event Reporting Requirements

Sites receiving monoclonal antibody will follow established mechanisms for tracking and reporting **serious adverse events**

- Events that are potentially attributable to monoclonal antibody use must be reported to the FDA
  - Refer to the Fact Sheet for Healthcare Providers as part of EUA for guidance
  - Complete and submit a MedWatch form or complete and fax FDA Form 3500 to report

Site must **maintain records** regarding use of the monoclonal antibody by patients

- **Inventory information:** e.g., lot numbers, quantity, receiving site, receipt date, product storage
- **Patient information:** e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered

Ensure that any records associated with this EUA are **maintained for inspection** upon request

Sites will report utilization daily or weekly through the mechanism indicated by their local, state, or territorial health department
mAb Administration Site Supplies Needed

**Infrastructure**
- Seating area with appropriate spacing for patients to receive mAb
- Steel table for product preparation
- Privacy screens if needed
- Protocol/outline for patient flow (written protocol not required however patient flow and infection control should be addressed at each administration site)
- Emergency response plan (written plan not required, however all staff should be aware of the plan for emergency response)

**General supplies**
- Infusion Reaction Kit
- Refrigerator
  - Optional to store prepared solution onsite
- Sharps container
- Biohazard disposal bag
- Trash bins and liners
- Disposable disinfecting wipes
- Hand sanitizer
- Thermometer probe covers (if required)
- 70% alcohol wipes
- Paper towels

**PPE**
- NIOSH-certified, disposable N95 filter facepiece respirators or better
- Gloves in appropriate sizes
- Gowns
- Surgical face masks for patients
- Eye and face protection (e.g. goggles, safety glasses, face shields)

**Administration Supplies-Subcutaneous**
- Alcohol wipes
- 3 or 5mL luer lock syringes (4 required for each patient for subcutaneous administration)
- Appropriate needles for product preparation and subcutaneous administration
  - 21 gauge 1.5 inch needles for product transfer
  - 25 or 27 gauge needles for subcutaneous administration (4 per each patient course)

**Administration Supplies-Intravenous**
- IV poles
- Alcohol wipes
- 2x2 gauze pads
- Adhesive bandages
- Medical tape
- Tegaderm bio-occlusive dressing
- Absorbent underpads (blue pads)
- Normal saline bags for mixing/administration- 50-250 mL
- IV administration sets: PVC infusion set with/without DEHP containing 0.2 or 0.22 micron polyethersulfone (PES) in-line filter
- IV catheters
- IV extension set tubing
- 3mL saline syringes
- Needles – stainless steel 18ga
- Optional: Transilluminator (vein finder)

**Patient Intake**
- Vital signs machine
- Pulse oximeter
- Thermometer
- Copies of eligibility checklist for treatment/ PEP

**Administrative**
- Site-specific documentation
- Patient fact sheets to provide each patient (copies in English, Spanish and other appropriate languages)
Module 5: Oral Therapeutic Administration
Patient Flow for Antiviral Oral Therapies
Scenario 1: Patient arrives at provider visit and medication available onsite

**Visit with Provider**

Confirm documentation of COVID-19 infection via either
- Participant-provided lab report
- Medical record lab report
- Direct communication from a provider or laboratory

Discuss treatment with patient
- Ensure patient meets treatment requirements and understands risks

Prescribe therapy for patient & provide the medication fact sheet
- Document required patient assessment in medical record
- Provide patient education on medication therapy being prescribed.

*Pre-treatment steps should be completed via telemedicine as possible (~30 mins)*

**Visit Discharge**

Medication and Fact Sheet provided to the patient
- Ensure patient is understands medication therapy being provided
- Ensure medication therapy being dispensed complies with federal/state dispensing laws.

**Post-visit**

Patient to begin prescribed therapy immediately and continue x 5 days

Patient to report any adverse effect to FDA MedWatch
- Patients that present for hospital visit may continue their prescribed antiviral during hospitalization (at discretion of provider).
Patient Flow for Antiviral Oral Therapies

Scenario 2: Patient arrives at provider visit and medication NOT available onsite

Visit with Provider

Confirm documentation of COVID-19 infection via either
- Participant-provided lab report
- Medical record lab report
- Direct communication from a provider or laboratory

Discuss treatment with patient
- Ensure patient meets treatment requirements and understands risks

Prescribe therapy for patient & provide the medication fact sheet
- Document required patient assessment in medical record
- Provide patient education on medication therapy being prescribed.

Determine locations medication is available in local area.

Visit Discharge

Prescription and Fact Sheet provided to the patient
- Ensure patient is understands medication therapy being prescribed
- Ensure patient is advised where to go pick up the medication therapy

Post-visit

Pharmacist receives or prescribes patient prescription
- Pharmacy should prioritize the prescription fill and ensure timely turnaround to support same day start for therapy.
- Pharmacist verifies prescription is appropriate for patient. Any concerns are clarified with prescribing provider.

Pharmacy staff dispenses product to the patient
- Patient is counseled on medication therapy and reminded to start immediately.

Patient to begin prescribed therapy immediately and continue x 5 days
Patient to report any adverse effect to FDA MedWatch
- Patients that present for hospital visit may continue their prescribed antiviral during hospitalization (at discretion of provider).

Module 6: Additional Resources
COVID-19 Vaccination after mAb Administration

Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the US

- Non-hospitalized COVID-19 patients who previously received passive antibody therapy
  - There is no longer any need to delay vaccination following receipt of monoclonal antibody or convalescent plasma beyond recovery from the acute illness (if symptoms were present) and criteria to discontinue isolation have been met.

- Hospitalized COVID-19 patients
  - Follow guidelines from CDC Advisory Committee on Immunization Practices: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#CoV-19-vaccination
Reporting Requirements

For sotrovimab**, bamlanivimab + etesevimab**, REGEN-COV**

Long Term Care / Skilled Nursing Facilities
Hospitals / Hospital Pharmacies
Non-hospital Facilities

Reporting required by 11:59 pm each Wednesday

For Evusheld, Paxlovid, bebtelovimab, Lagevrio (molnupiravir)

Hospitals / Hospital Pharmacies

HPOP

Reporting required twice per week by 11:59 pm Monday and Thursday

**Not currently authorized for use anywhere in the U.S. due to the prevalence of non-susceptible SARS-CoV-2 variant

Sites administering/dispensing USG-purchased COVID-19 therapeutics must provide information on product utilization and stock on hand.
Thank you!

Questions?
https://ASPR.HHS.gov
covid19therapeutics@hhs.gov