COVID-19 Vaccines & Therapies (Clinician Info Session)

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STATE OF MAINE
Department of
Health and Human Services

COVID-19 Vaccines

Updates—Vaccines

- FDA approved Moderna COVID-19 vaccine for individuals 18+ years

- For people with moderate/severe immunocompromise:
  - Clarified recommendations for 3 doses of mRNA vaccine + booster dose
  - Shortened primary series-booster interval from 5 months to 3 months
  - For people who got J&J vaccine: additional dose + booster dose (3 total)

- For all people who received a passive antibody product (such as a monoclonal antibody or plasma—with/without immunocompromise)
  - No longer necessary to delay vaccination after passive antibody treatment

CDC: *COVID-19 Vaccines for Moderately or Severely Immunocompromised People* (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html), Updated February 17, 2022

CDC updates on COVID-19 vaccines

- Extended interval between the 1st and 2nd mRNA COVID-19 vaccine dose

- Updates to CDC's Interim Clinical Considerations:
  - Vaccination schedule
  - Guidance for people who are moderately to severely immunocompromised
  - Guidance on COVID-19 vaccination and passive antibody product use

- Summary of current recommendations for COVID-19 vaccination by age group

Updated Guidance Passive Antibody Products

- Updated guidance
  - **No recommended deferral period**
  - However, **tixagevimab/cilgavimab (EVUSHELD™)** should be deferred for at least two weeks after vaccination
- Previous guidance was to defer COVID-19 vaccination for
  - 30 days if product used for post exposure prophylaxis
  - 90 days if product used for treatment

Recommendations for the Interval Between the First and Second mRNA COVID-19 Vaccine Doses

- Some people ages 12 through 64 years—and especially males ages 12 through 39 years—may benefit from getting their second mRNA COVID-19 vaccine dose **8 weeks** after receiving their first dose
- Providers should continue to recommend the **3-week** (Pfizer-BioNTech) or **4-week** (Moderna) interval for patients who:
  - Are at higher risk of having an inadequate response to the first mRNA vaccine dose
    - People who are moderately or severely immunocompromised
  - Are at higher risk for severe COVID-19
    - Adults ages 65 years and older
  - Need rapid protection, such as during high levels of community transmission
  - Children ages 5–11 years

General Recommendations

- COVID-19 primary series vaccination is recommended for **everyone ages 5 years and older** in the United States for the prevention of COVID-19
  - This includes people both with and without **underlying medical conditions**
  - People with **moderate or severe immunocompromise** have additional considerations and need **more** doses than most people.
- In most situations, **Pfizer-BioNTech** or **Moderna** COVID-19 vaccines are preferred over the Janssen COVID-19 vaccine for primary and booster vaccination.

Figure 1. COVID-19 Vaccination Schedule*

Vaccine	0 month	1 month	2 month	3 month	4 month	5 month	6 month	7 month
Pfizer-BioNTech (ages 5–11 years)	1st dose	2nd dose (3 weeks after 1st dose						
Pfizer-BioNTech (ages 12 years and older)	1st dose	2nd dose† (3-8 weeks after 1st dose)					Booster dose‡ (at least 5 months after 2nd dose)	
Moderna (ages 18 years and older)	1st dose	2nd dose† (4-8 weeks after 1st dose)					Booster dose‡ (at least 5 months after 2nd dose)	
Janssen (ages 18 years and older)	1st dose		Booster dose‡ (at least 2 months after 1st dose)					

Note: Timeline is approximate. Intervals of 3 months or fewer are converted into weeks per the formula "1 month = 4 weeks". Intervals of 4 months or more are converted into calendar months.

* See Guidance for COVID-19 vaccination for people who are moderately or severely immunocompromised for schedule for people who are moderately or severely immunocompromised.

† An 8-week interval may be optimal for some people ages 12 years and older, especially for males ages 12 to 39 years. A shorter interval (3 weeks for Pfizer-BioNTech; 4 weeks for Moderna) between the first and second doses remains the recommended interval for: people who are moderately or severely immunocompromised; adults ages 65 years and older; and others who need rapid protection due to increased concern about community transmission or risk of severe disease.

‡ An mRNA COVID-19 vaccine is preferred over the Janssen COVID-19 Vaccine for booster vaccination of people ages 18 years and older. For people ages 12–17 years, only Pfizer-BioNTech can be used. People ages 5–11 years should not receive a booster dose.

02/23/22

Figure 2. COVID-19 Vaccination Schedule for People Who Are Moderately or Severely Immunocompromised

Vaccine	0 month	1 month	2 month	3 month	4 month	5 month
Pfizer-BioNTech (ages 5–11 years)	1st dose	2nd dose (3 weeks after 1st dose)	3rd dose (at least 4 weeks after 2nd dose)			
Pfizer-BioNTech (ages 12 years and older)	1st dose	2nd dose (3 weeks after 1st dose)	3rd dose (at least 4 weeks after 2nd dose)		Booster dose* (at least 3 months after 3rd dose)	
Moderna (ages 18 years and older)	1st dose	2nd dose (4 weeks after 1st dose)	3rd dose (at least 4 weeks after 2nd dose)			Booster dose* (at least 3 months after 3rd dose)
Janssen (ages 18 years and older)	1st dose	2nd (additional) dose† using an **mRNA COVID-19 vaccine** (at least 4 weeks after 1st dose)		Booster dose* (at least 2 months after additional dose)		

Note: Timeline is approximate. Intervals of 3 months or fewer are converted into weeks per the formula "1 month = 4 weeks". Intervals of 4 months or more are converted into calendar months.

* An mRNA COVID-19 vaccine is preferred over the Janssen COVID-19 Vaccine for booster vaccination of people ages 18 years and older. For people ages 12–17 years, only Pfizer-BioNTech can be used. People ages 5–11 years should not receive a booster dose.

† Only Pfizer-BioNTech or Moderna COVID-19 Vaccine should be used. See Appendix B for more information on vaccinating people who are moderately or severely immunocompromised and who received Janssen COVID-19 Vaccine for the primary series.

02/23/22

COVID-19 Therapies

Updates—Therapeutics

- 2/25: sotrovimab EUA: treat within 7 days after symptom onset
- 2/25: EVUSHELD dose increased to 300mg + 300mg, recommendation for catch-up dose for those who only received 150mg + 150mg earlier
- 2/18: Maine expands EVUSHELD for PrEP eligibility to Categories 1–4
- 2/11: FDA authorizes bebtelovimab, a new monoclonal antibody drug

Evusheld EUA Update

Updated Evusheld Dosing Requirements (tixagevimab and cilgavimab)

Initial Dosage and Administration	Repeat Dosing for Patients who Previously Received 150 mg tixagevimab and 150 mg of cilgavimab
300 mg of tixagevimab and **300 mg of cilgavimab** administered as two separate consecutive intramuscular injections.	**150 mg of tixagevimab** and **150 mg of cilgavimab** administered as two separate intrmuscular injections as soon as possible.

For more information, see *Fact Sheet for Healthcare Providers: Emergency Use Authorization For EVUSHELD (tixagevimab co-packaged with cilgavimab).*

Sotrovimab EUA Update

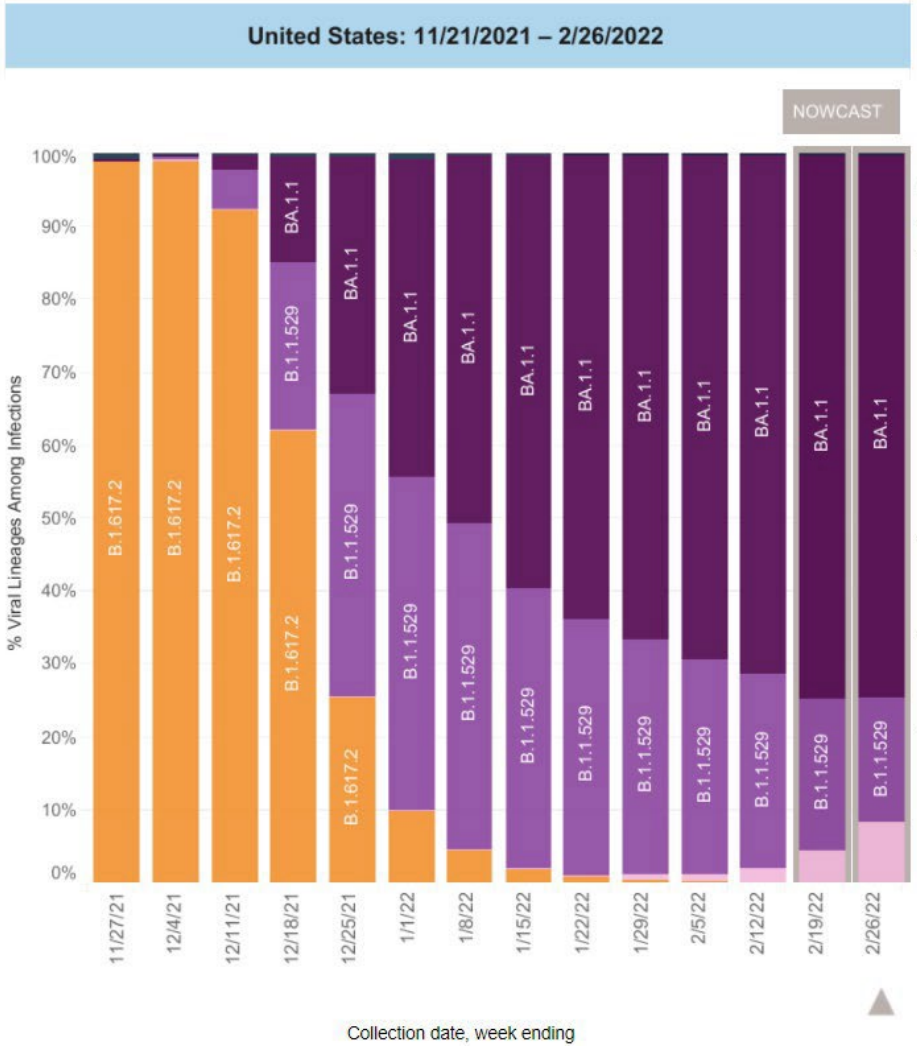
- For adults and pediatric patients (12 years of age and older weighing at least 40 kg): **500 mg** administered as a **single IV infusion <u>over 15 minutes for 50-mL</u>** infusion bag or **<u>30 minutes for 100-mL</u>** infusion bag.
- Sotrovimab should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and **within 7 days** of symptom onset.
- Sotrovimab is not authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency.
  - Sotrovimab demonstrated 16-fold reduction in susceptibility to BA.2 variant via pseudovirus assay; clinical relevance is unknown

CMS Updates: Coding for Bebtelovimab and Remdesivir

- CMS created new codes, effective Feb. 11, 2022
- Q0222:
  Long descriptor: Injection, bebtelovimab, 175 mg
  Short descriptor: Bebtelovimab 175
- M0222:
  Long Descriptor: IV injection, bebtelovimab, includes injection and post administration monitoring
  Short Descriptor: Bebtelovimab injection
- M0223:
  Long Descriptor: Intravenous injection, bebtelovimab, includes injection and post administration monitoring in the home or residence; this includes a beneficiary's home that has been made provider-based to the hospital during the covid-19 public health emergency
  Short Descriptor: Bebtelovimab injection home
- Updated FAQs – Payment/Coding for Veklury (Remdesivir) (begin pg 146/question 30)
- Visit the CMS COVID-19 Monoclonal Antibodies Toolkit for more information

Prevalence of COVID-19 Variants Nationally

- HHS and CDC actively monitoring variant prevalence nationally



United States: 2/20/2022 – 2/26/2022 NOWCAST

USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	BA.1.1	VOC	74.6%	70.3-78.4%
	B.1.1.529	VOC	17.2%	14.1-20.8%
	BA.2	VOC	8.3%	6.3-10.7%
Delta	B.1.617.2	VOC	0.0%	0.0-0.0%
Other	Other*		0.0%	0.0-0.0%

* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed.

** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates

\# AY.1-AY.133 and their sublineages are aggregated with B.1.617.2. BA.1 and BA.3 are aggregated with B.1.1.529. For regional data, BA.1.1 is also aggregated with B.1.1.529, as it currently cannot be reliably called in each region.

https://covid.cdc.gov/covid-data-tracker/#variant-proportions

Outpatient Therapeutic Portfolio

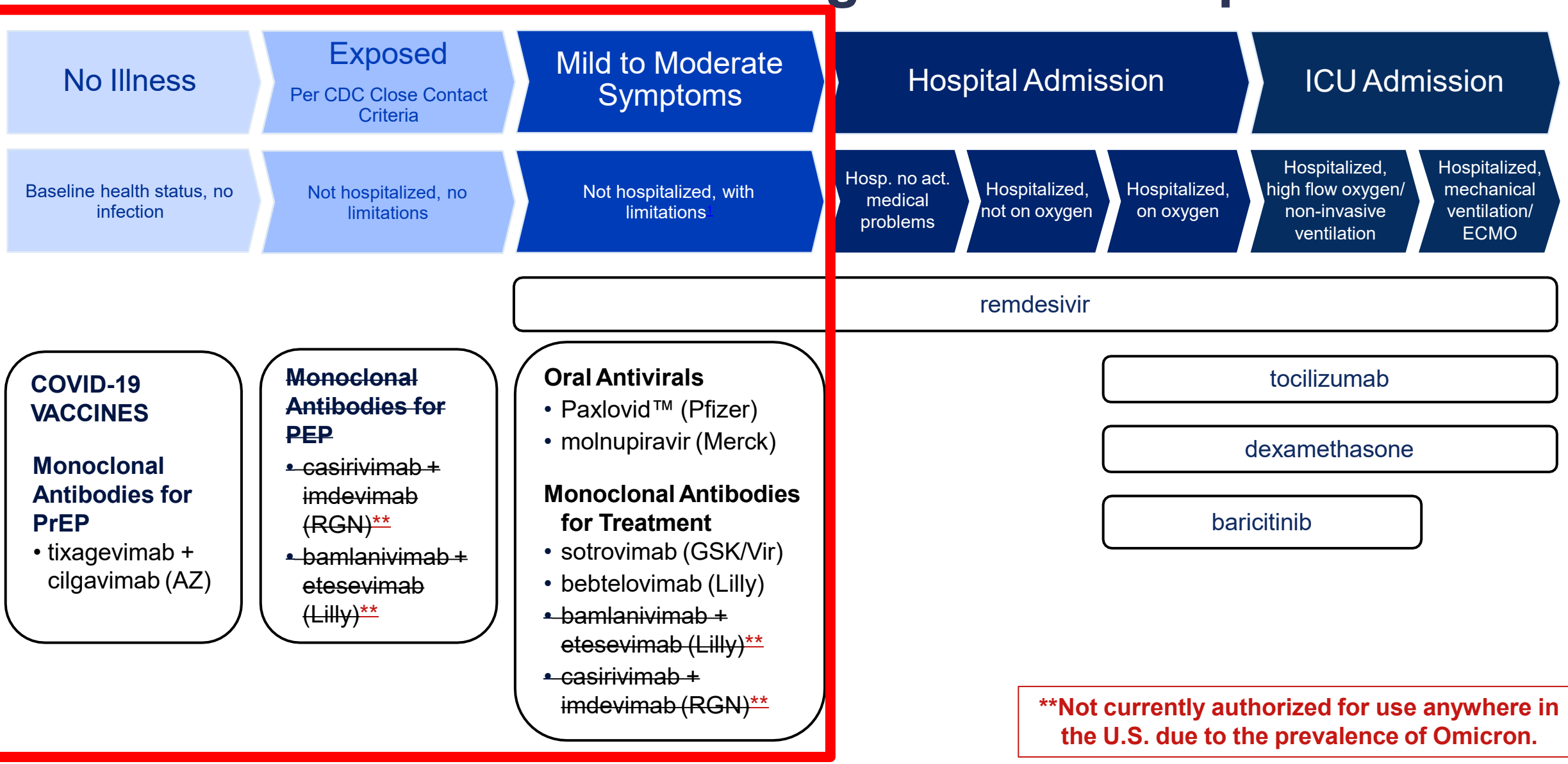
For Planning Purposes Only – Subject to Change

	Drug Class	Allocation Cadence*	Sweep Schedule*	Allocation Feb 7	Allocation Feb 14	Planned Allocation Feb 21	Planned Allocation Feb 28	Planned Allocation Mar 7	Planned Allocation Mar 14
Paxlovid Pfizer	Oral antiviral	Transition to Weekly	N/A	100,000	0	150,000	0	125,000	125,000
Molnupiravir Merck	Oral antiviral	Transition to Weekly	N/A	400,000	+ requests	350,000 (+ requests)	+ requests	125,000 (+ requests)	125,000 (+ requests)
Sotrovimab GSK/Vir	Monoclonal for treatment	Weekly	N/A	52,250	52,250	52,250	47,000	52,250	52,250
Bebtelovimab Lilly	Monoclonal for treatment	Weekly	N/A	N/A	49,000	49,000	52,000	49,000	49,000
Evusheld AstraZeneca	Monoclonal for prevention	Transition to Monthly	N/A	50,000	50,000	50,000	50,000	200,000 (monthly allocation)	(ordering against monthly)
Bam/Ete Lilly	Monoclonal; omicron resistance	Weekly	Weekly; Saturday	Distribution pause[1]	Distribution pause[1]	Distribution pause[1]	Distribution pause[1]	Distribution pause[1]	Distribution pause[1]
REGEN-COV Regeneron	Monoclonal, omicron resistance	Weekly	Weekly; Saturday	Distribution pause[1]	Distribution pause[1]	Distribution pause[1]	Distribution pause[1]	Distribution pause[1]	Distribution pause[1]
Remdesivir Gilead	IV antiviral	Commercial Market	N/A	N/A	N/A	N/A	N/A	N/A	N/A

1. In accordance with the FDA EUA update on 1/24/2022, bam/ete and REGEN-COV distribution is paused nationally due to the high prevalence of the omicron variant. Resumption of allocation will be considered based on variant prevalence data and/or availability of patient level variant diagnostic testing.

* As disease incidence declines and incoming supply increases to better meet demand, allocation strategies may transition later in March.

COVID-19 Preventative Agents & Therapeutics

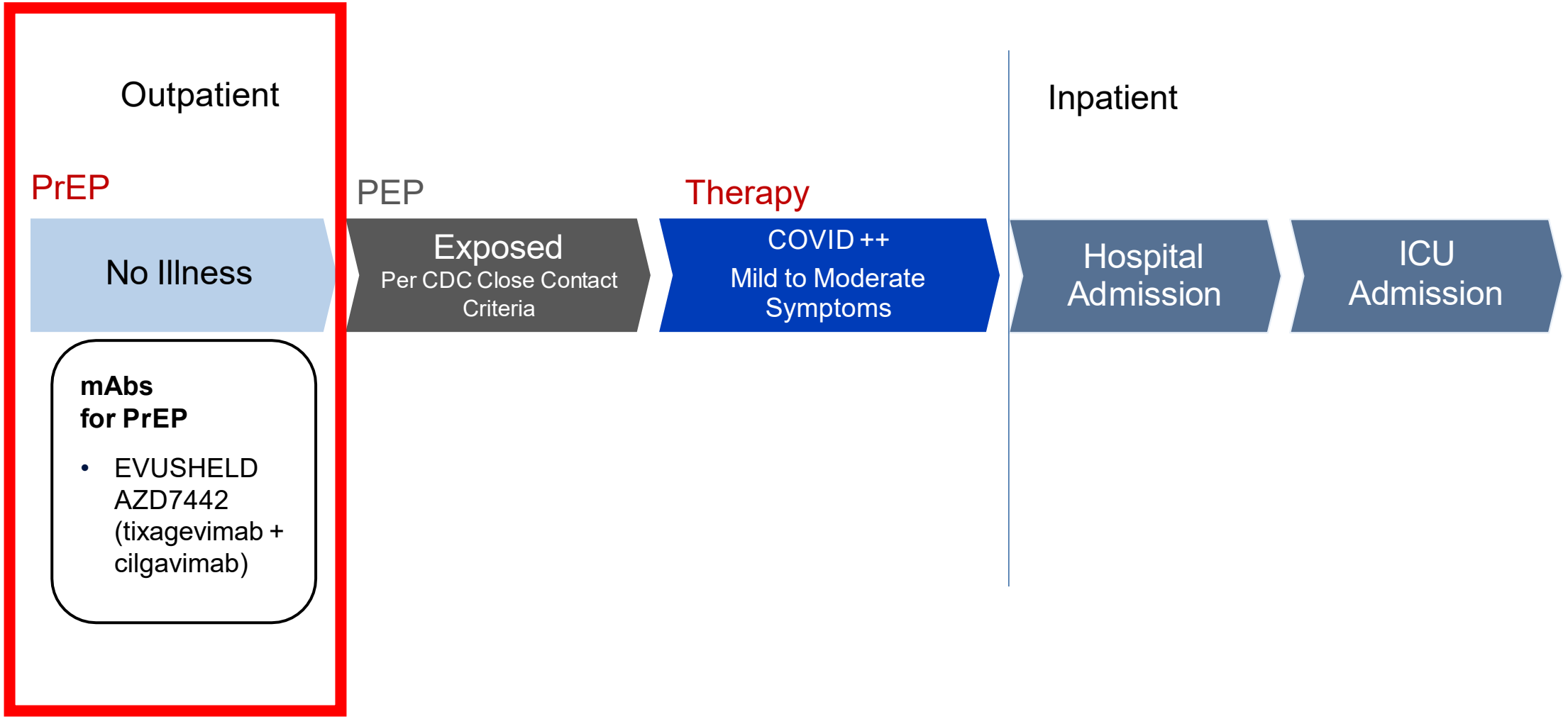


**Not currently authorized for use anywhere in the U.S. due to the prevalence of Omicron.

[1] NIH COVID-19 Treatment Guidelines https://www.covid19treatmentguidelines.nih.gov/about-the-guidelines/whats-new/
Therapeutic Management of Nonhospitalized Adults With COVID-19 https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults--therapeutic-management/

Pre-exposure Prophylaxis (PrEP)

Stages of COVID-19 Therapeutics



EVUSHELD™ (tixagevimab and cilgavimab) – AstraZeneca
Monoclonal Antibody for IM Injection

[EVUSHELD Product Information]

https://www.evusheld.com

EVUSHELD™ 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:
  - NIH COVID-19 Treatment Guidelines Panel's Statement on Therapies for High-Risk, Nonhospitalized Patients https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults--therapeutic-management/
  - COVID-19 Therapeutics Locator: https://covid-19-therapeutics-locator-dhhs.hub.arcgis.com/
  - FDA MedWatch: https://www.fda.gov/medwatch/report.htm
  - 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).

Fact Sheet for Health Care Providers Emergency Use Authorization for Evusheld (tixagevimab co-packaged with cilgavimab (https://www.fda.gov/media/154701/download)

EVUSHELD™ (tixagevimab and cilgavimab): Limitations of Authorized Use

- EVUSHELD™ is not authorized for use:
  - *For treatment of COVID-19.*
  - *For PEP of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.*
- PrEP with EVUSHELD™ 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™ should be administered at least 2 weeks after last vaccination.
- EVUSHELD™ may only be prescribed by a healthcare provider licensed under state law to prescribe drugs for an individually identified patient and who has the education and training to make the clinical assessment necessary for appropriate use of EVUSHELD™.

[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

- ~~150 mg~~ 300 mg **of tixagevimab** and ~~150 mg~~ 300 mg **of cilgavimab** administered as two separate consecutive intramuscular injections.
  - preferably one in each of the gluteal muscles, one after the other

Contraindications and Precautions

- History of severe hypersensitivity reactions, including anaphylaxis, to any component of EVUSHELD™.
- Administer with caution to people with any coagulation disorder and at high risk for cardiovascular events.

For more information, see *Fact Sheet for Healthcare Providers: Emergency Use Authorization For EVUSHELD™ (tixagevimab co-packaged with cilgavimab)* (https://www.fda.gov/media/154701/download)

Eligibility & Prioritization for COVID-19 PrEP

Maine Category 1

- Lung Transplant Recipient (any time frame)
- Small Bowel Recipient (any time frame)
- Receipt of the following immunosuppressive medication within the past 12 months (for any condition, oncology and non-oncology):
  - Anti-thymocyte globulin (ATG)
  - Alemtuzumab
  - Anti-B-Cell Therapy: Rituximab, Ocrelizumab, Ofatumumab
- B-Cell Malignancies, on active treatment (e.g., B-cell lymphomas, chronic lymphocytic leukemia, acute B-cell lymphoblastic leukemia, etc.)
- Multiple Myeloma, on active treatment with two or more agents
- Allogeneic Stem Cell Transplant, within 12 months of Transplant
- Autologous Stem Cell Transplant, within 6 months of Transplant
- Recipient of more than one active Transplant, different Organs (any time frame)
- Acute Myeloid Leukemia under Active Treatment
- Receipt of anti-CD19 or anti-BCMA (CAR)-T-Cell Immunotherapy, within six months of treatment
- Primary or Secondary T-Cell Immunodeficiency, including Severe Combined Immunodeficiency:
  - Agammaglobulinemia (XLA/ARAG)
  - Common Variable Immunodeficiency (CVID) and similar phenotype with T-cell dysfunction
  - Defects of Innate Immunity with predominant susceptibility to Viral Infections (e.g., WHIM Syndrome)
- Additional pediatric conditions (age 12–17 years):
  - Combined immune deficiencies with or without immune dysregulation (e.g., APDS, STAT3 GOF, ALPS)
  - Primary immune regulatory disorders with or without immune deficiency (e.g., APECED, XIAP)
  - High-risk or relapsed acute lymphoblastic leukemia/lymphoblastic lymphoma on intensive therapy (not maintenance therapy)

Maine Category 2

- Allogeneic stem cell transplant, more than 12 months since transplant
- Autologous stem cell transplant, more than 6 months since transplant
- Multiple myeloma, on maintenance therapy
- Any solid tumor, on active myelosuppressive chemotherapy
- Any solid organ transplant recipient not otherwise eligible in Category 1
- Other chronic leukemias, on treatment
- *Patients in lower categories with more than one qualifying condition*

Maine Category 3

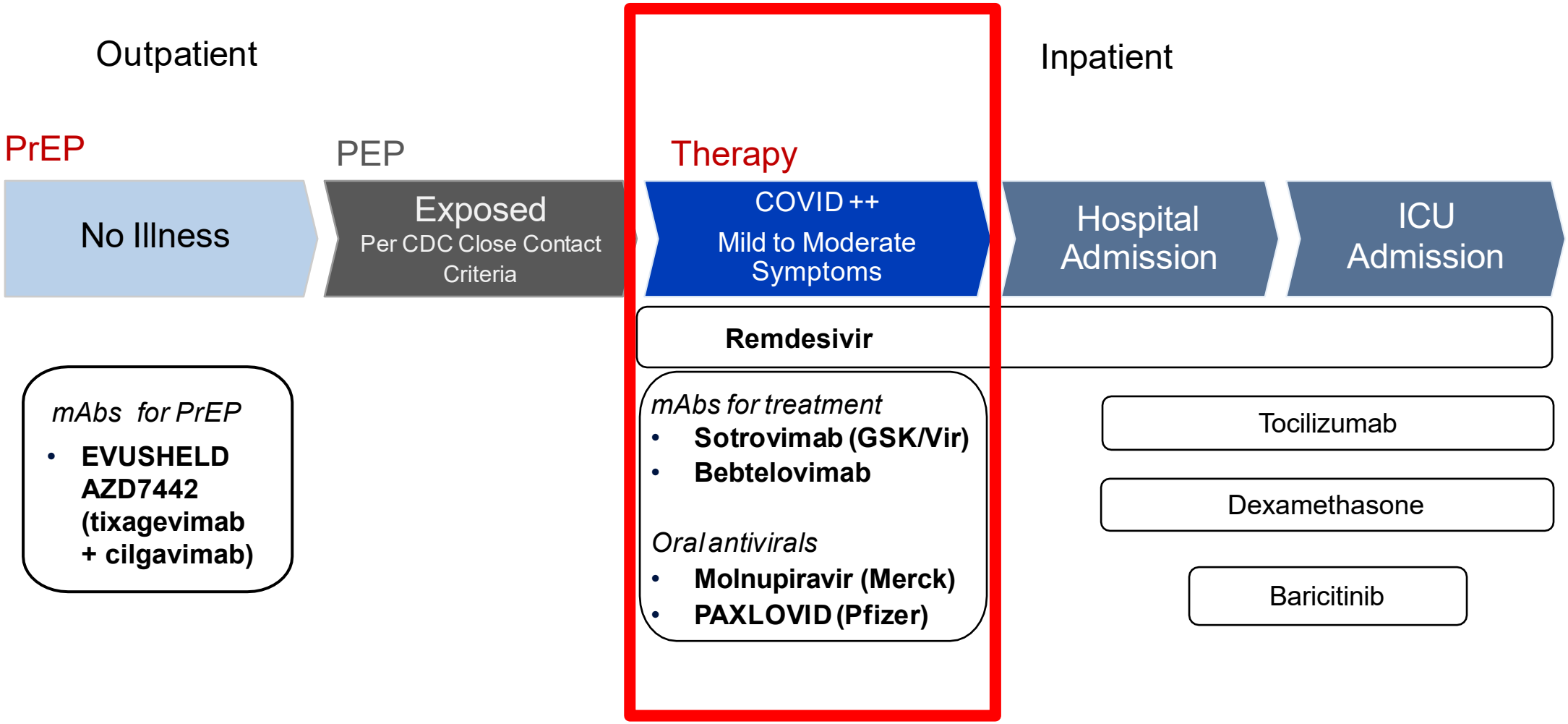
- Active treatment with high-dose corticosteroids (i.e., more than 20 mg prednisone or equivalent per day when administered for two weeks or longer)
- Active treatment with other biologic agents that are immunosuppressive or immunomodulatory, not otherwise listed in Categories 1–2
- Advanced or untreated HIV infection:
  - HIV with CD4 less than 200/mm^3 (if aged less than 14 years, CD4% less than 15%)
  - AIDS-defining illness

Maine Category 4

- Persons 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).

Treatments and Prioritization

Stages of COVID-19 Therapeutics



Eligibility Criteria for 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 40kg
- 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)**

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

1. CDC: Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Providers (https://www.cdc.gov/coronavirus/2019- ncov/hcp/clinical-care/underlyingconditions.html)

*Patient eligibility with respect to time since symptom onset varies across agents. See product fact sheets for product-specific durations.

US CDC: People with Certain Medical Conditions

- Cancer
- Chronic kidney disease
- Chronic liver disease
- Chronic lung diseases
- Cystic Fibrosis
- Dementia or other neurological conditions
- Diabetes (type 1 or type 2)
- Disabilities
- Heart conditions
- HIV infection
- Immunocompromised state (weakened immune system)
- Mental health conditions
- Overweight and obesity
- Physical inactivity
- Pregnancy
- Sickle cell disease or thalassemia
- Smoking, current or former
- Solid organ or blood stem cell transplant
- Stroke or cerebrovascular disease
- Substance use disorders
- Tuberculosis
- Children with medical complexity

US CDC: People with Certain Medical Conditions (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html)

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

Higher risk for severe COVID-19 outcomes

- Cancer
- Cerebrovascular disease
- Chronic kidney disease*
- *Chronic lung diseases:*
  Interstitial lung disease, Pulmonary embolism, Pulmonary hypertension, Bronchiectasis, COPD (chronic obstructive pulmonary disease)
- *Chronic liver diseases:*
  Cirrhosis, Non-alcoholic fatty liver disease, Alcoholic liver disease, Autoimmune hepatitis
- Cystic fibrosis
- Diabetes mellitus, type 1 and type 2*
- *Disabilities:*
  Attention-Deficit/Hyperactivity Disorder (ADHD): Cerebral Palsy, Congenital Malformations (Birth Defects), Limitations with self-care or activities of daily living, Intellectual and Developmental Disabilities, Learning Disabilities, Spinal Cord Injuries, other disabilities [full list on webpage]
- Heart conditions (e.g., heart failure, coronary artery disease, or cardiomyopathies)
- HIV (human immunodeficiency virus)
- *Mental health disorders:*
  Mood disorders (including depression), Schizophrenia spectrum disorders
- Neurologic conditions limited to dementia
- Obesity (BMI ≥30 kg/m^2)*
- Primary Immunodeficiencies
- Pregnancy and recent pregnancy
- Physical inactivity
- Smoking, current and former
- Solid organ or hematopoietic cell transplantation
- Tuberculosis
- Use of corticosteroids or other immunosuppressive medications

Suggestive higher risk for severe COVID-19 outcomes

- Children with certain underlying conditions
- Overweight (BMI ≥25 kg/m^2, but <30 kg/m^2)
- Sickle cell disease
- Substance use disorders
- Thalassemia

Mixed evidence

- Alpha 1 antitrypsin deficiency
- Asthma
- Bronchopulmonary dysplasia
- Hepatitis B
- Hepatitis C
- Hypertension*

** indicates underlying conditions for which there is evidence for pregnant and non-pregnant people*

US CDC: Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals (https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html)

Comparisons of Recommended Outpatient Therapies

	Paxlovid™	Sotrovimab	Bebtelovimab	Remdesivir	Molnupiravir
Age allowed for use	≥ 12 yr	≥ 12 yr	≥ 12 yr	≥ 12 yr*	≥18 yr
Initiate within # days of symptom onset	< 5 days	< 7 days	< 7 days	< 7 days	< 5 days
Route of Administration	PO	IV	IV	IV	PO
Duration of Therapy	5 days	1 time	1 time	3 days	5 days
Pros	-High efficacy -Oral	-High efficacy -Single IV infusion	-High efficacy -Single IV infusion	-High efficacy -Greater experience	-Oral -No drug-drug interaction concerns
Cons	Ritonavir-related drug-drug interactions	Requires IV infusion	Requires IV infusion	-Requires 3 days of IV infusion	-Low efficacy -Not authorized for age 12-17 years -Not approved for pregnancy -Concerns for mutagenicity
Supply Availability	Limited supply	Limited supply	Limited supply	Commercially available	Greater than Paxlovid

*

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

Is Patient:
- Hospitalized for COVID-19 **OR**
- Requiring O_2 **OR**
- An increase in baseline home O_2 due to COVID-19

No

Symptom onset within the past 5-7 days?

Yes

No

Treatment of symptoms, Management per NIH & CDC Guidelines

Yes

Does patient have severe renal impairment (eGFR <30mL/min) **OR** severe hepatic impairment (Child-Pugh Class C)

Yes

Consider:

sotrovimab[4] 500 mg IV begun **ASAP within 7 days of symptom onset**

OR

bebtelovimab[5] 175 mg single IV injection **ASAP within 7 days of symptom onset.**

No

Consider one of the following therapeutics, if available:[1]

PAXLOVID[2] within **5 days of symptom onset**

- **eGFR ≥60 mL/min :** 300 mg nirmatrelvir taken with 100 mg ritonavir twice daily for 5 days
- **eGFR ≥30-<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[2,3]

OR

sotrovimab[4] 500 mg IV begun **ASAP within 7 days of symptom onset** OR

bebtelovimab[5] 175 mg single IV injection **ASAP within 7 days of symptom onset** OR

remdesivir[6] 200mg IV x 1 dose on Day 1, 100mg IV x 1 on Days 2-3 begun **ASAP within 7 days of symptom onset**

If none of these therapeutics are available or clinically appropriate for patient treatment:

No

Is patient age 18 or older AND possibility of pregnancy, if applicable, ruled out?

Yes

Consider molnupiravir[7] 800mg 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 **molnupiravir EUA**[7]

References:

[1] NIH's COVID-19 Treatment Guidelines Panel's Statement on Therapies for High-Risk, Non-hospitalized Patients With Mild to Moderate COVID-19. https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-high-risk-nonhospitalized-patients/

[2] PAXLOVID EUA. https://www.fda.gov/media/155050/download

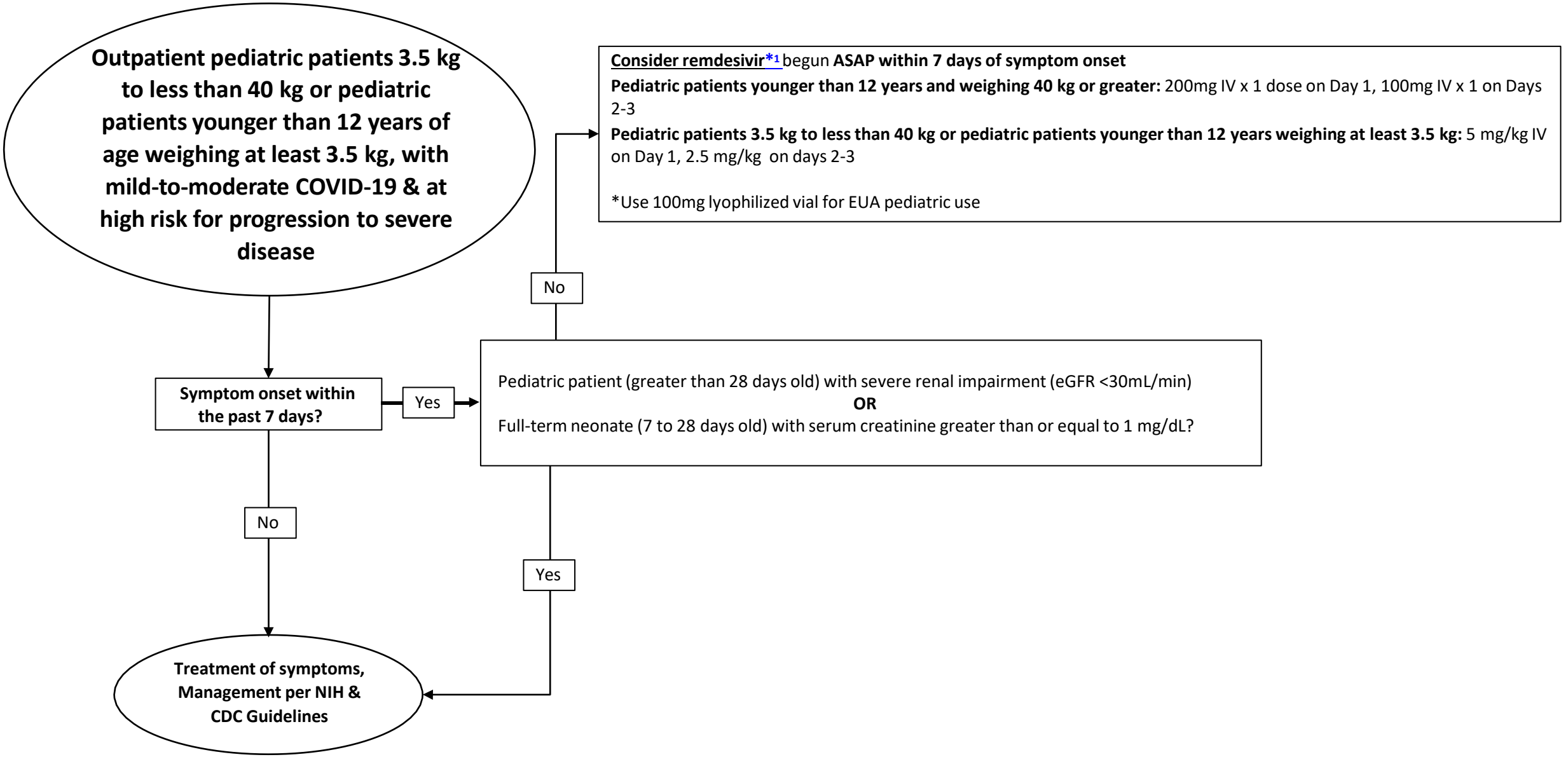
[3] NIH's COVID-19 Treatment Guidelines Panel's Statement on Potential Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications. https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-paxlovid-drug-drug-interactions/

[4] Sotrovimab EUA. https://www.fda.gov/media/149534/download

[5] Bebtelovimab EUA. https://www.fda.gov/media/156152/download

[6] Veklury (remdesivir) Prescribing Information. https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf

[7] Molnupiravir EUA. https://www.fda.gov/media/155054/download



February 24, 2022

Reference:

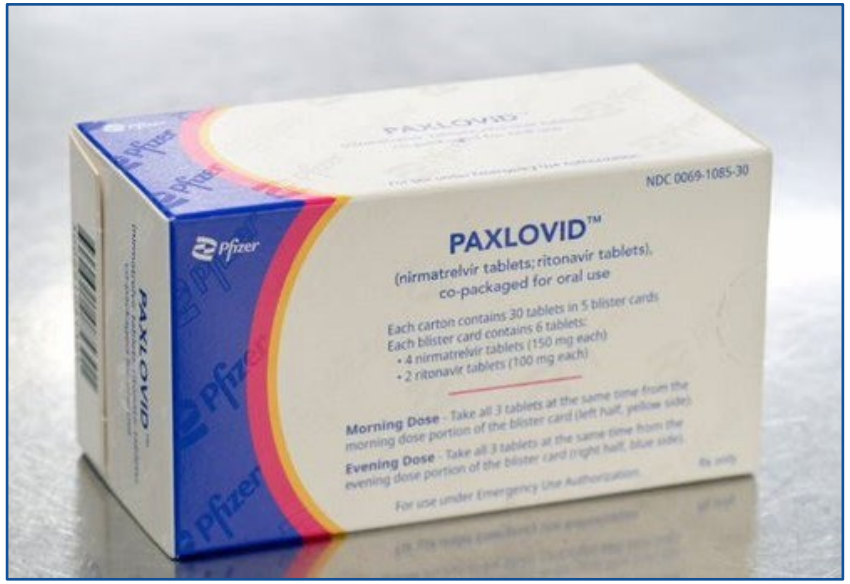
[1] Remdesivir EUA: https://www.fda.gov/media/137566/download.

Frequently Asked Questions Related to EUA

- Products under EUA must be administered in accordance with the EUA.
- A signed consent form is not needed to administer products under EUA.
- No clinical data reporting is required beyond established FDA mechanisms for tracking and reporting serious adverse events.

Products for Treatment of Mild-to-Moderate COVID-19

Paxlovid™ (nirmatrelvir and ritonavir) – Pfizer
Oral Antiviral



[Paxlovid Product Information]
https://www.pfizer.com/products/product-detail/paxlovidtm

Paxlovid™ 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:
  - Website for Healthcare Providers: https://www.covid19oralrx-hcp.com/
  - Website for Patients: https://www.covid19oralrx-patient.com/
  - Pharmacist Instruction Sheet: https://www.covid19oralrx-hcp.com/files/Clean_EUA-105-mitigation-plan-for-moderate-renal-impairment-01-11-22.pdf

- Additional Resources:
  - NIH COVID-19 Treatment Guidelines Panel's Statement on Therapies for High-Risk, Nonhospitalized Patients https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults--therapeutic-management/
  - COVID-19 Therapeutics Locator: https://covid-19-therapeutics-locator-dhhs.hub.arcgis.com/
  - FDA MedWatch: https://www.fda.gov/medwatch/report.htm
  - Safety Reporting: http://www.pfizersafetyreporting.com/
  - Module 5 Oral Therapeutics Administration

Paxlovid™ 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 40kg) 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™ 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 Paxlovid belongs (i.e., anti-infectives).

Fact Sheet for Health Care Providers Emergency Use Authorization of Paxlovid (https://www.fda.gov/media/155050/download)

Paxlovid™

Dosage and Administration

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

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™ 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™ 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, see *Fact Sheet for Healthcare Providers: Emergency Use Authorization For PAXLOVID*.
(https://www.fda.gov/media/155050/download)

Paxlovid™ Provider Checklist

- ❑ Positive SARS-CoV-2 test
- ❑ Age ≥12 years
- ❑ Weight ≥40 kg
- ❑ High-risk criteria met
- ❑ Symptoms consistent with mild-moderate COVID-19
- ❑ Symptom onset with **5 days***
- ❑ Not hospitalized due to COVID-19
- ❑ If clinically indicated, assess patient renal function
  - eGFR ≥60 mL/min, standard dosing
  - eGFR ≥30 to <60 mL/min, dose modification
  - eGFR <30 mL/min, not recommended
- ❑ If clinically indicated, assess patient hepatic function
  - Child-Pugh Class C, contraindicated
- ❑ **Assess patient's home medication list for drug-drug interactions**
  - See next slide for more detail

*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™ Contraindications*

Hypersensitivity Reactions	• History of clinically significant hypersensitivity reactions (e.g., TEN, SJS) to its active ingredients (nirmatrelvir or ritonavir) or any other components of the product
Drugs highly dependent on CYP3A4 for clearance and for which elevated concentrations are associated with severe/life-threatening reactions*	• Alpha1-adrenoreceptor antagonists: alfuzosin • Analgesics: pethidone, piroxicam, propoxyphene • Antianginal: ranolazine • Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine • Anti-gout: colchicine • Antipsychotics: lurasidone, pimozide, clozapine • Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine • HMG-CoA reductase inhibitors: lovastatin, simvastatin • PDE5 inhibitor: sildenafil (Revatio) when used for PAH • Sedative/hypnotics: triazolam, oral midazolam
Drugs that are potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir concentrations may be associated with loss of virologic response or resistance*	• Anticancer drugs: apalutamide • Anticonvulsant:: carbamazepaine, phenobarbital., phenytoin • Antimycobacterials: rifampin • Herbal product: St John's Wort (*hypericum perforatum)*

***NOT COMPLETE LIST OF ALL DDI's. ALWAYS USE CLINICAL TOOLS/DDI CHECKER AND USE CLINICAL JUDGMENT** https://covid19-druginteractions.org/view_all_interactions
For additional information see: NIH COVID-19 Treatment Guidelines Panel's Statement on Paxlovid Drug-Drug Interactions (https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-paxlovid-drug-drug-interactions/)

Paxlovid provider fact sheet: https://www.fda.gov/media/155050/download

Paxlovid™ Renal Adjustment Instructions for Pharmacists

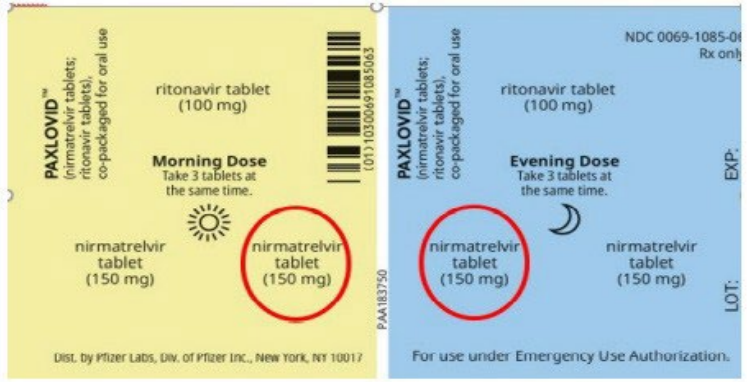


Figure 1: Remove the nirmatrelvir tablets circled in red from the blister card

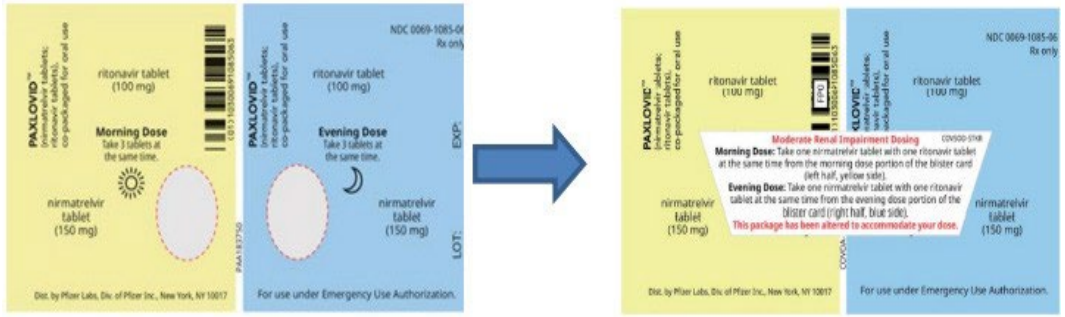


Figure 2: Placement of sticker over empty blister cavities and pre-printed dosing instruction after removal of nirmatrelvir tablets

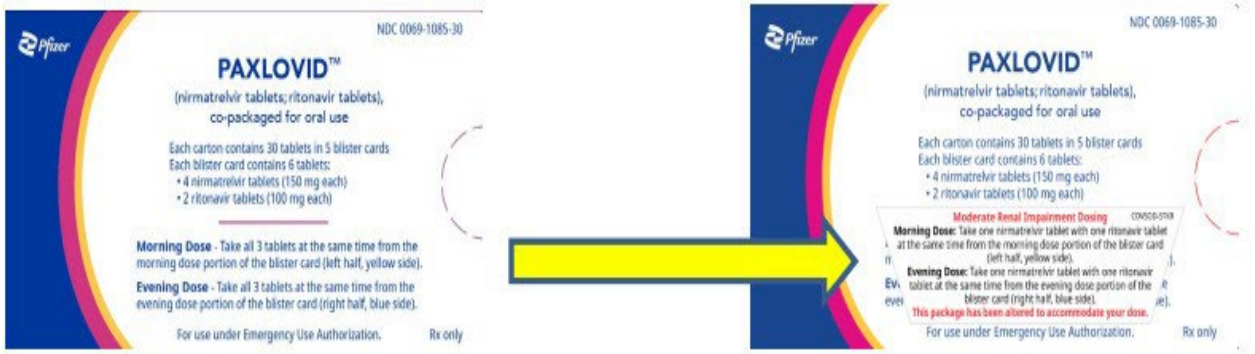


Figure 3: Placement of sticker over pre-printed dosing regimen on carton

Pharmacist Instruction Sheet: https://www.covid19oralrx-hcp.com/files/Clean_EUA-105-mitigation-plan-for-moderate-renal-impairment-01-11-22.pdf

Sotrovimab – GSK/Vir
Monoclonal Antibody for IV Infusion

[sotrovimab Product Information]

https://www.sotrovimab.com

Sotrovimab Product Information

- FDA Fact Sheets
  - sotrovimab provider fact sheet: https://www.fda.gov/media/149534/download
  - sotrovimab patient fact sheet: https://www.fda.gov/media/149533/download
  - sotrovimab patient fact sheet (Spanish): https://www.sotrovimab.com/content/dam/cf-pharma/hcp-sotrovimab-phase2/en_US/sotrovimab- eua-fact-sheet-for-patients-in-spanish.pdf

- Manufacturer's Resources:
  - Website for Healthcare Providers: https://www.sotrovimab.com/
  - Website for Patients: https://www.sotrovimab.com/patient

- Additional Resources:
  - NIH COVID-19 Treatment Guidelines Panel's Statement on Therapies for High-Risk, Nonhospitalized Patients https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults--therapeutic-management/
  - Therapeutics Distribution https://protect-public.hhs.gov/pages/therapeutics-distribution
  - FDA MedWatch: https://www.fda.gov/medwatch/report.htm
  - **Safety Reporting Email**: WW.GSKAEReportingUS@gsk.com
  - Module 4 Monoclonal Antibody Administration

Sotrovimab Authorization

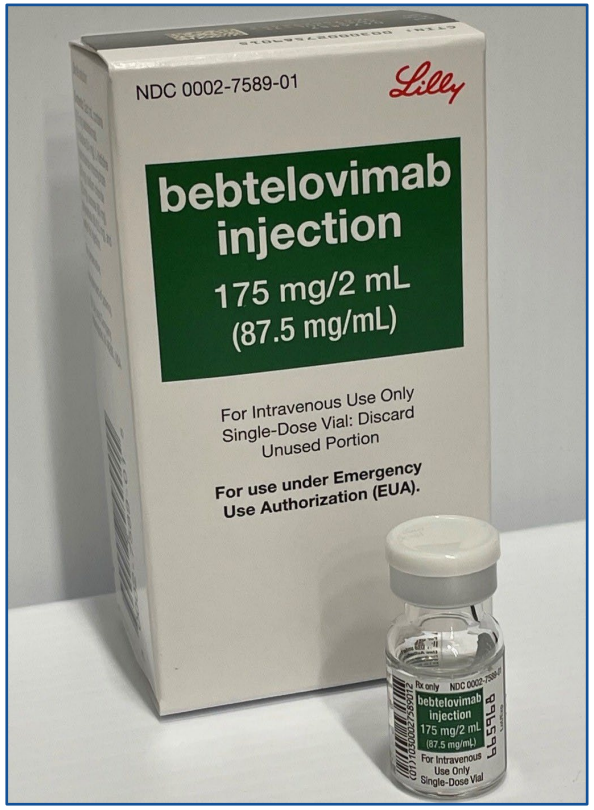
- FDA has issued an EUA to permit the emergency use of sotrovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg):
  - With positive results of direct SARS-CoV-2 viral testing, **AND**
  - Who are at high risk for progression to severe COVID-19, including hospitalization or death.
- Sotrovimab 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).

Fact Sheet for Healthcare Providers Emergency Use Authorization (EUA) of sotrovimab
https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Sotrovimab/pdf/SOTROVIMAB-EUA.PDF#nameddest=HCPFS

Sotrovimab Dosage and Administration

- For adults and pediatric patients (12 years of age and older weighing at least 40 kg): **500 mg** administered as a **single IV infusion over 30 minutes**.
- Sotrovimab injection should be prepared by a qualified healthcare professional using aseptic technique.
- Sotrovimab should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within ~~10~~ **7 days** of symptom onset.

Bebtelovimab – Eli Lilly
Monoclonal Antibody for IV Injection (IV Push)



[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: http://www.lillyantibody.com/bebtelovimab
  - Website for Patients: http://www.lillyantibody.com/bebtelovimab
- Additional Resources:
  - NIH COVID-19 Treatment Guidelines Panel's Statement on Therapies for High-Risk, Nonhospitalized Patients https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults--therapeutic-management/
  - https://covid-19-therapeutics-locator-dhhs.hub.arcgis.com/ https://covid-19-therapeutics-locator-dhhs.hub.arcgis.com/
  - FDA MedWatch: https://www.fda.gov/medwatch/report.htm
  - **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
- 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 see *Fact Sheet for Healthcare Providers: Emergency Use Authorization For bebtelovimab*.

https://www.fda.gov/media/156152/download

Bebtelovimab Dosage and Administration

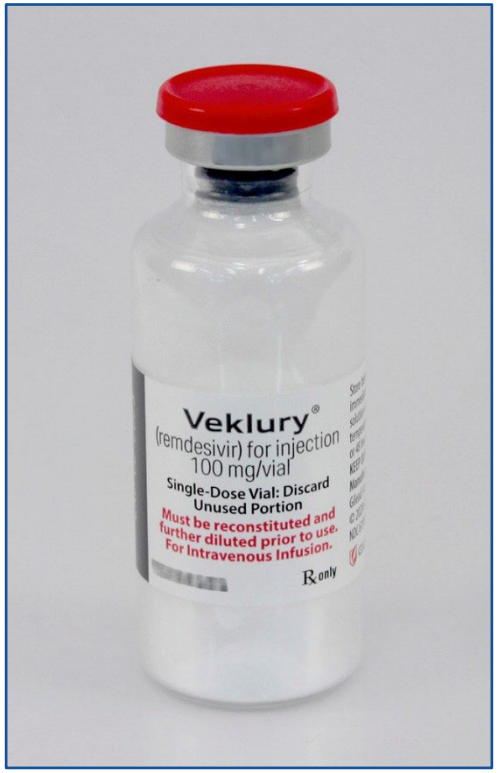
- For adults and pediatric patients (12 years of age and older weighing at least 40 kg): **175 mg** administered as a **single IV injection (i.e., IV push) over at least 30 seconds**.
- Bebtelovimab injection should be prepared by a qualified healthcare professional using aseptic technique.
- Bebtelovimab 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 see *Fact Sheet for Healthcare Providers: Emergency Use Authorization 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
- Attach the syringe extension set.
- Prime the 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.

Veklury® (remdesivir) – Gilead
Antiviral for IV Infusion



Veklury Product Information
https://www.vekluryhcp.com/

Veklury® (remdesivir) Product Information

- Prescribing Information & FDA Fact Sheets
  - Veklury (remdesivir) Prescribing Information: https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf
  - remdesivir provider fact sheet: https://www.fda.gov/media/137566/download
  - remdesivir patient fact sheet: https://www.fda.gov/media/137565/download
  - remdesivir patient fact sheet (Spanish): https://www.fda.gov/media/139460/download

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

- Additional Resources:
  - NIH COVID-19 Treatment Guidelines Panel's Statement on Therapies for High-Risk, Nonhospitalized Patients https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults--therapeutic-management/
  - FDA MedWatch: https://www.fda.gov/medwatch/report.htm
  - **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 (12 years of age and older who weigh at least 40 kilograms) 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
- FDA also revised EUA to authorize Veklury® (remdesivir) for treatment of certain **non-hospitalized pediatric** patients:
  - weighing 3.5 kilograms to less than 40 kilograms **OR**
  - pediatric patients less than 12 years of age weighting at least 3.5 kilograms, 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) Prescribing Information: https://www.gilead.com/-/media/files/pdfs/medicines/COVID-19/veklury/veklury_pi.pdf

remdesivir provider fact sheet: https://www.fda.gov/media/137566/download

Veklury® (remdesivir)

Dosage and Administration

- Dosage:
  - For adults and pediatric patients 12 years of age and older weighing more than 40kg: **200 mg** on Day 1, followed by once-daily maintenance doses of **100 mg** from Day 2 and Day 3 administered only via intravenous infusion over 30 to 120 minutes[1]
  - For pediatric patients weighing 3.5 kg to <40 kg: **5 mg/kg** on Day 1 followed by **2.5 mg/kg** once daily Days 2-3[2]
- Dosage Forms:
  - For injection: **100 mg** of remdesivir as a lyophilized powder, in a single-dose vial
  - Injection: **100 mg/20mL (5mg/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

For more information, see [1]*Fact Sheet for Healthcare Providers: Emergency Use Authorization For Veklury* (https://www.fda.gov/media/137566/download) *and* [2]*Veklury Prescribing Information* (https://www.gilead.com/-/media/files/pdfs/medicines/COVID-19/veklury/veklury_pi.pdf)

Molnupiravir – Merck
Oral Antiviral

Molnupiravir Product Information
https://www.molnupiravir-us.com/

Molnupiravir Product Information

- FDA Fact Sheets
  - molnupiravir provider fact sheet: https://www.fda.gov/media/155054/download
  - molnupiravir patient fact sheet: https://www.fda.gov/media/155055/download
  - molnupiravir patient fact sheet (Spanish): https://www.fda.gov/media/155115/download

- 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:
  - NIH COVID-19 Treatment Guidelines Panel's Statement on Therapies for High-Risk, Nonhospitalized Patients https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults--therapeutic-management/
  - COVID-19 Therapeutics Locator: https://covid-19-therapeutics-locator-dhhs.hub.arcgis.com/
  - FDA MedWatch: https://www.fda.gov/medwatch/report.htm
  - **Safety Reporting Email:** dpoc.usa@msd.com
  - Module 5 Oral Therapeutics Administration

Molnupiravir Authorization

- Molnupiravir has been authorized by FDA under an EUA, for the treatment of mild-to-moderate COVID-19 in adults who are at high-risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options 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

- 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 molnupiravir belongs (i.e., anti-infectives).

Fact Sheet for Health Care Providers Emergency Use Authorization of Molnupiravir (https://www.fda.gov/media/155054/download)

Molnupiravir

Dosage and Administration

- **800 mg** (**four 200 mg** capsules) taken orally every 12 hours for 5 days, with or without food.
- 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 molnupiravir authorized under this EUA.
- Not recommended for use during pregnancy and not authorized for use in patients under 18 years of age.

For more information, see *Fact Sheet for Healthcare Providers: Emergency Use Authorization For Molnupiravir*.
https://www.fda.gov/media/155054/download

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 molnupiravir*
  - Breastfeeding is not recommended for the *duration of treatment and for **4 days** after the last dose of 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*

*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.

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 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 molnupiravir*
   - Breastfeeding is not recommended for the *duration of treatment and for **4 days** after the last dose of 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*
5. The prescribing healthcare provider and/or the provider's designee must report all medication errors and serious adverse events potentially related to molnupiravir within 7 calendar days from the healthcare provider's awareness of the event

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

Molnupiravir Prescriber Requirements

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 molnupiravir use during pregnancy
   - Document* that the patient is aware of the known and potential benefits and potential risks of 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 molnupiravir 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.**

Pathway to Treatment: 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 **5 to 10 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

Onset of symptoms	Clinical visit and diagnostic test	Confirmed positive test	Treatment
	***≤ 3 days** post symptom onset*	***≤ 24 hours** post diagnostic test*	***ASAP** post positive test result*

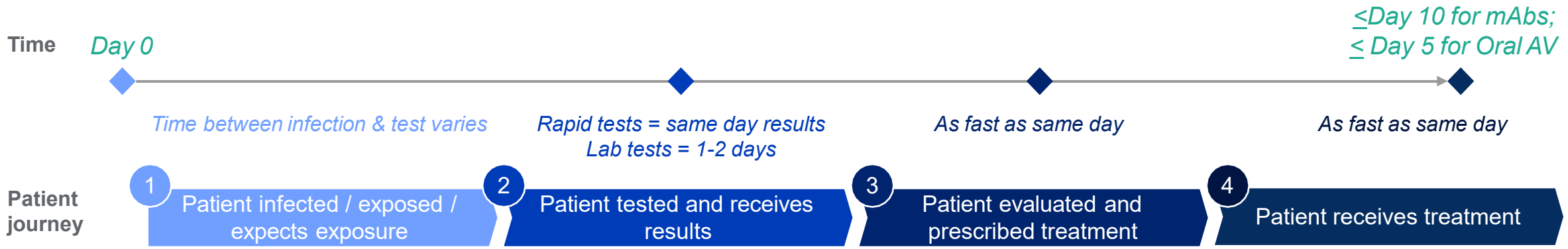
Treatment required within 5 to 10 days of symptom onset *Testing sites should recommend COVID+ patients that are high risk confer with their HCP on potential suitability for Tx*

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

Planning required for "Test to Treat" models

***Please reference EUA factsheet for specific treatment guidelines including recommended treatment window**

Minimize Leakages in the Patient Journey Around Awareness & Access



Potential awareness leakage points	• Patient asymptomatic • Patient does not inform close contacts of potential exposure	• Patient unaware of / doesn't believe in need to test • Patient unaware of time window; waits too long to test	• Patient unaware of Tx options • Patient unaware of time window; waits too long to see HCP • Provider unaware of drug or reluctant to prescribe	• Patient unaware of time window; waits too long to fill Rx
Potential access leakage points		• No rapid test available at site • Lab takes too long returning results	• Patient cannot access provider consult	• Patient can't access product (e.g., cannot find site, site does not have product, delivery takes too long)

COVID-19 Test to Treat Strategy: Overall Goals

- Facilitate **early diagnosis and rapid linkage to treatment** for individuals with COVID-19 who are at **high risk for complications.**
- Prevent disease progression and transmission through early diagnosis and treatment of high-risk individuals, thereby **reducing morbidity and mortality** caused by COVID-19
- **Reduce disparities in COVID-19 outcomes** through equitable strategies that prioritize access to tests and reduce barriers to treatments for high-risk individuals disproportionately impacted by COVID-19

Test to Treat Overview

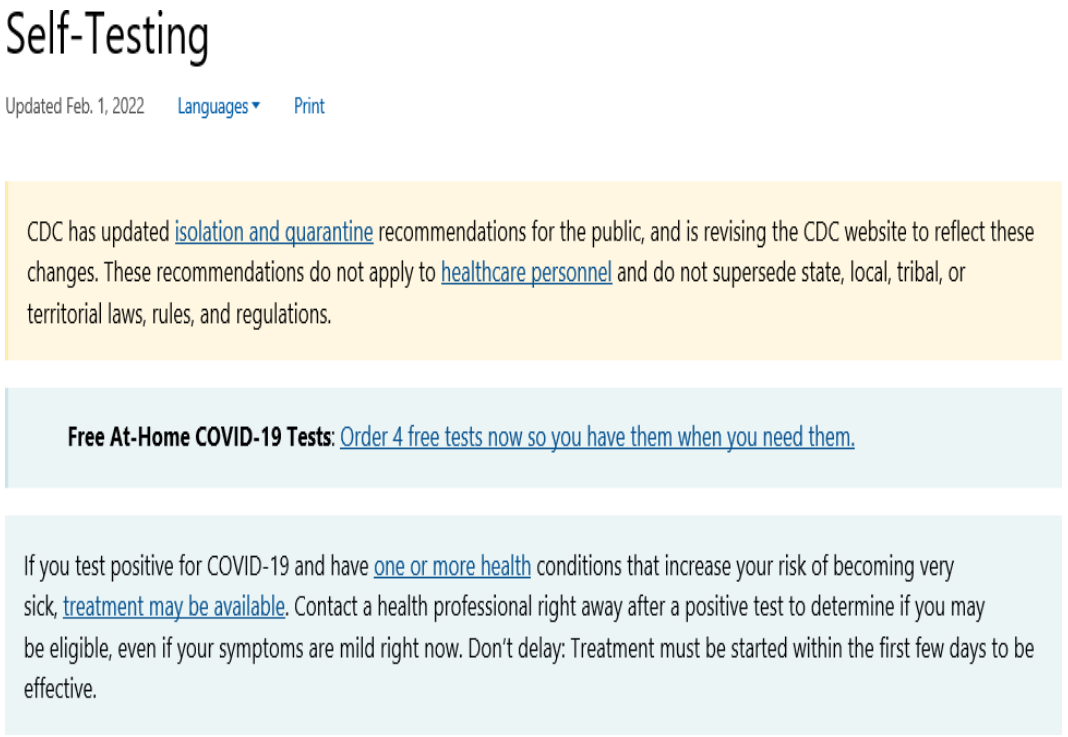
- ***Test to Treat efforts aim to address challenges with patients obtaining therapeutics, <u>including</u>:***
  - Consumer knowledge of “test to treat” guidance
  - Access to tests upon symptom onset
  - Access to healthcare provider (or treatment site for mAbs) within timeframe for treatment effectiveness
  - Provider knowledge of and comfort level with prescribing therapeutics
  - Equitable distribution of therapeutics, especially in the setting of limited supply
  - Provider/consumer locating site with medication in-stock

COVID-19 Test to Treat Strategy: Overall Goals

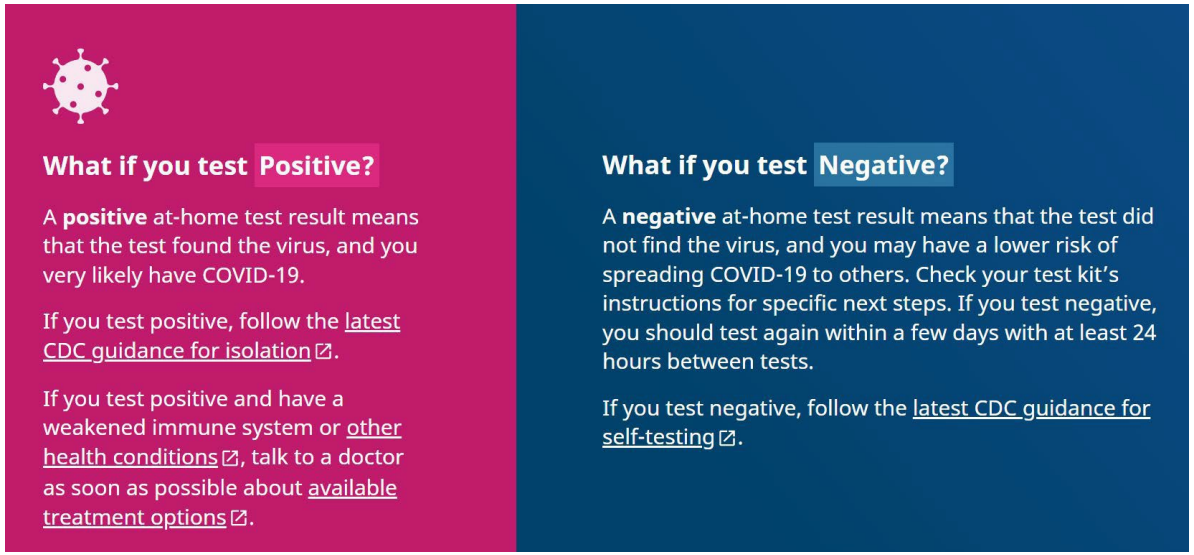
- **Increase COVID-19 test and treat health literacy.**
- **Ensure Access to Tests** for early diagnosis, with a specific focus on high-risk individuals.
- **Facilitate Rapid Linkage to Care after Positive Result**, with a specific focus on high-risk individuals.
- **Ensure Access to Therapeutics,** with a focus on equitable distribution.

Increase COVID-19 Test to Treat Health Literacy

- Include Test to Treat language on testing websites

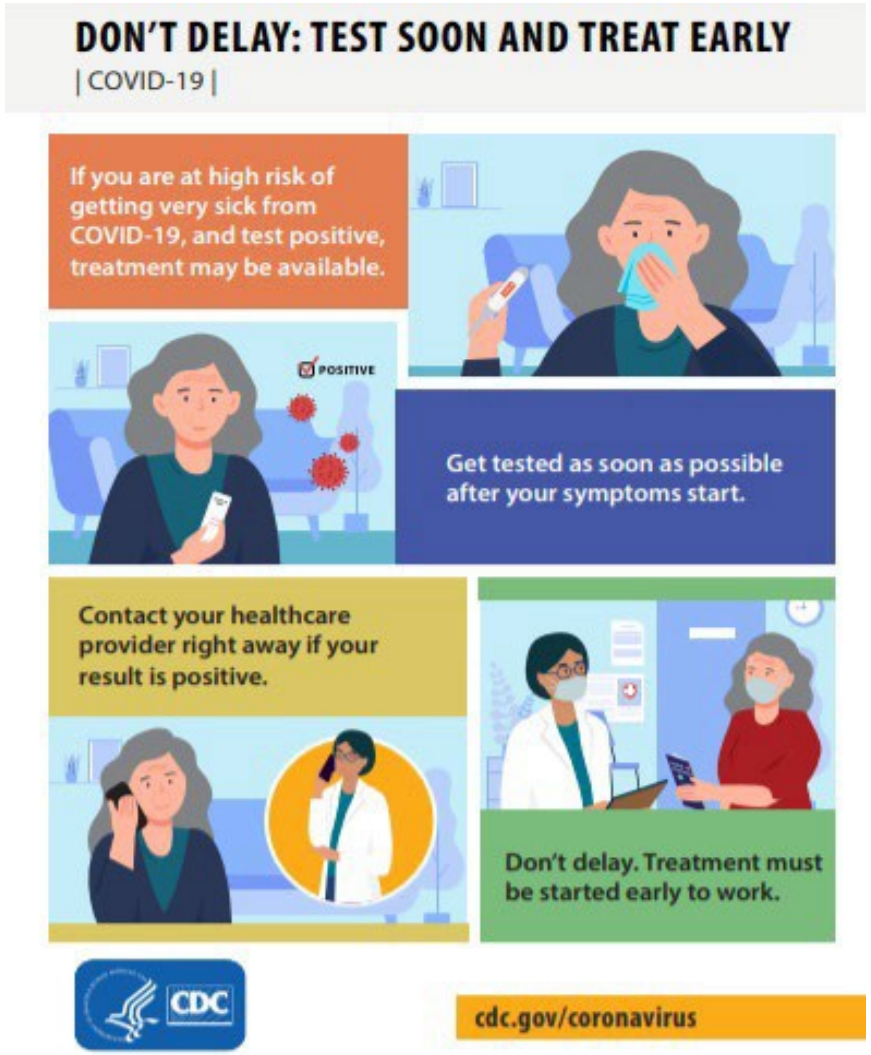


https://www.cdc.gov/coronavirus/2019-ncov/testing/self- testing.html



https://www.covidtests.gov/

Increase COVID-19 Test to Treat Health Literacy



https://www.cdc.gov/coronavirus/2019-ncov/downloads/communication/print-resources/Test-Soon-Treat-Early.pdf

Test to Treat Models

- **Goal of Test to Treat:** Facilitate **early diagnosis and rapid linkage to treatment** for individuals with COVID-19 who are at **high risk for complications**, thereby **reducing morbidity and mortality** caused by COVID-19 and r**educing disparities in COVID-19 outcomes.**
- **Requirements for successful Test to Treat model for Oral Antivirals:**
  - Awareness by patient and provider of current testing and treatment guidance and availability.
  - Rapid access to test and results after symptom onset.
  - Timely access to a healthcare provider for evaluation and prescription.*
  - Timely access to medication (within a few days after symptom onset.)

**Different requirement for mAbs*

Test to Treat Initiative

- **Promote and support a variety of existing and new pathways for increased public and provider awareness, rapid access to tests, and/or linkage to treatment, including:**
    - Public education campaign and enhanced patient/consumer education and messaging
    - Provider outreach to increase knowledge of and comfort level with prescribing therapeutics
    - Ensuring access to and prepositioning tests in high priority settings & populations
    - Ensuring access to and prepositioning therapeutics in high priority settings and populations
        - HRSA-funded health centers
        - Working with states/territories to support efforts re: distribution to high priority locations
        - Prioritize other settings in which end-to-end test to treat model can be provided and/or disease burden is high
    - Ongoing efforts to increase supply of therapeutics
    - Exploring further opportunities for telehealth and other options for linkage to care and treatment

COVID-19 Therapies in Maine

NIH: COVID-19 Treatment Guidelines When There Are Logistical or Supply Constraints

- Interim statement to provide guidance on which individuals might receive the greatest benefit from anti-SARS-CoV-2 therapeutics for treatment or prevention.

- **Prioritization:**
  - **Treatment** of COVID-19 over PEP of SARS-CoV-2 infection
  - Treatment of COVID-19 in **unvaccinated** or **incompletely vaccinated individuals** with clinical risk factors for severe illness and vaccinated individuals who are not expected to mount an adequate immune response
  - Use of tixagevimab plus cilgavimab (EVUSHELD) as PrEP for **severely immunocompromised individuals** over moderately immunocompromised individuals

[1] COVID-19 Treatment Guidelines, See NIH Statement on Patient Prioritization for Outpatient Therapies

NIH Risk Group Prioritization Criteria

The Panel prioritized the following risk groups for anti-SARS-CoV-2 mAb therapy based on **Age**, **Vaccination status**, **Immune status**, and **Clinical risk factors**

- For a list of risk factors, see the CDC webpage Underlying Medical Conditions
- Associated with High Risk for Severe COVID-19

- The CDC website COVID-19 Vaccines for Moderately or Severely Immunocompromised People provides a list of moderate and severe immunocompromising conditions.

- If supplies cannot be provided to all moderately to severely immunocompromised individuals because of logistical constraints or supply limitations, the Panel suggests prioritizing their use for those who are least likely to mount an adequate response to COVID-19 vaccination or SARS-CoV-2 infection and who are at risk for severe outcomes.

[1] COVID-19 Treatment Guidelines, See NIH Statement on Patient Prioritization for Outpatient Therapies

COVID-19 Therapeutics in Maine

Drug	Route	Duration	Start timing	Access*	Supply	Offer to
Paxlovid	Oral	5 days	0–5 days after symptom onset	Pharmacies, Hospitals, Clinics	**Very good**	**Maine Tiers 1–3**
sotrovimab	IV	1 day	0–7 days after symptom onset	Hospitals, Clinics	**Very good**	**Maine Tiers 1–3**
bebtelovimab	IV	1 day	0–7 days after symptom onset	Hospitals, Clinics	**Very good**	**Maine Tiers 1–3**
remdesivir	IV	3 days	0–7 days after symptom onset	Hospitals, Clinics	**Excellent**	**Maine Tiers 1–3**
molnupiravir	Oral	5 days	0–5 days after symptom onset	Pharmacies, Hospitals, Clinics	**Very good**	**Maine Tiers 1–3**

**For information on sites offering treatments in Maine, see the COVID-19 Treatment in Maine patient information webpage.*
(https://www.maine.gov/dhhs/mecdc/infectious-disease/epi/airborne/coronavirus/covid19-treatment.shtml)

Recommended Prioritization for COVID-19 Therapeutics

In the setting of limited supply of therapeutics, prioritize use of treatments as follows:

Maine Tier 1	**Moderately/Severely Immunocompromised***** **Unvaccinated* or Vaccinated*, 75+ years** **Unvaccinated*, 50+ years, 1+ clinical risk factors**** **Unvaccinated, Pregnant⁺**
Maine Tier 2	**Unvaccinated*, 65+ years** **Vaccinated*, 65+ years, 1+ clinical risk factors**** **Unvaccinated* or Vaccinated*, 2+ risk factors**** **Residing in a congregate facility⁺⁺**
Maine Tier 3	**All other patients per EUA or prescriber information**

⁺Pregnant:
Treat all pregnant COVID-19 patients who are unvaccinated. Also consider treatment in the postpartum period. Consider treating vaccinated persons with other risk factors. Avoid use of antivirals if other drugs are available.

⁺⁺Congregate facility:
Includes persons living in nursing homes, assisted living facilities, jails prisons, and homeless shelters who do not meet higher-level criteria.

****Unvaccinated** refers to an individual who has not received 2 doses of an mRNA vaccine or 1 dose of the J&J vaccine. **Vaccinated** refers to an individual who received 2 doses of an mRNA vaccine or 1 dose of the J&J vaccine. Vaccinated individuals who have not received a vaccine booster dose are likely at higher risk for severe disease than those who are boosted, and providers may choose to prioritize such patients for treatment.*

***Clinical risk factors:** some of the most important Underlying Medical Conditions Associated with High Risk for Severe COVID-19 (US CDC) include cancer, cardiovascular disease, chronic kidney disease, chronic lung disease, diabetes, immunocompromising conditions or receipt or immunosuppressive medications, obesity (BMI ≥30), pregnancy, sickle cell disease.*

****Immunocompromising conditions:** Moderately or Severely Immunocompromised People (US CDC) include people who have been receiving active cancer treatment for tumors or cancers of the blood, received an organ transplant and are taking medicine to suppress the immune system, received a stem cell transplant within the last 2 years or taking medicine to suppress the immune system, moderate or severe primary immunodeficiency (such as DiGeorge syndrome, Wiskott-Aldrich syndrome), advanced or untreated HIV infection, or active treatment with high-dose corticosteroids or other drugs that suppress the immune response.*

NIH: Preference Based on Efficacy and Convenience of Use

NIH: Dosing Regimens for the Drugs Recommended for High-Risk, Nonhospitalized Adults With Mild to Moderate COVID-19, Listed in Order of Preference Based on Efficacy and Convenience of Use

Drug Name	Dosing Regimen	Time From Symptom Onset[a]
Ritonavir-Boosted Nirmatrelvir (Paxlovid)	•**eGFR ≥60 mL/min:** Nirmatrelvir 300 mg with RTV 100 mg PO twice daily for 5 days •**eGFR ≥30 to <60 mL/min:** Nirmatrelvir 150 mg with RTV 100 mg PO twice daily •**eGFR <30 mL/min: Not recommended** •**Severe Hepatic Impairment (Child-Pugh Class C): Not recommended**	≤5 days
Sotrovimab	SOT 500 mg as a single IV infusion	≤10 days
Remdesivir	RDV 200 mg IV on Day 1, followed by RDV 100 mg IV once daily on Days 2 and 3[b,c]	≤7 days
Molnupiravir	Molnupiravir 800 mg PO twice daily for 5 days	≤5 days

[a] Per EUA criteria or clinical trial entry criteria.
[b] An eGFR <30 mL/min at screening or <90 days before screening was considered an exclusion criterion in the outpatient RDV study PINETREE, but only if a participant's weight was <48 kg. See the Remdesivir section for a discussion of RDV use in patients with renal impairment.
[c] If RDV is administered to patients who have a new or increasing need for supplemental oxygen but who are discharged from the ED because hospital resources are limited and inpatient admission is not possible, the total duration of therapy is ≤5 days.
Key: ED = emergency department; eGFR = estimated glomerular filtration rate; EUA = Emergency Use Authorization; IV = intravenous; PO = orally; RDV = remdesivir; RTV = ritonavir; SOT = sotrovimab

[1] COVID-19 Treatment Guidelines, See NIH Statement on Patient Prioritization for Outpatient Therapies

Selection Considerations for Clinical Options

Order	Drug	Effectiveness (hosp/death)	Eligibility*	Start within	Benefits	Challenges
#1	**Paxlovid**	88%	12 years (40 kg)	5 days	Oral drug	Drug-drug interactions Severe shortage
#2	**sotrovimab**	85%	12 years (40 kg)	7 days	Single treatment	IV infusion x1 day Severe shortage
#3	**bebtelovimab**	Unknown	12 years (40 kg)	7 days	Single treatment	IV infusion x1 day Severe shortage
#4	**remdesivir**	87%	12 years (40 kg) <12 y, 3.5–40 kg**	7 days	Abundant supply	IV infusion x3 days Insurance Transportation
#5	**molnupiravir**	30%	18 years	5 days	Oral drug	Avoid in pregnancy Moderate shortage

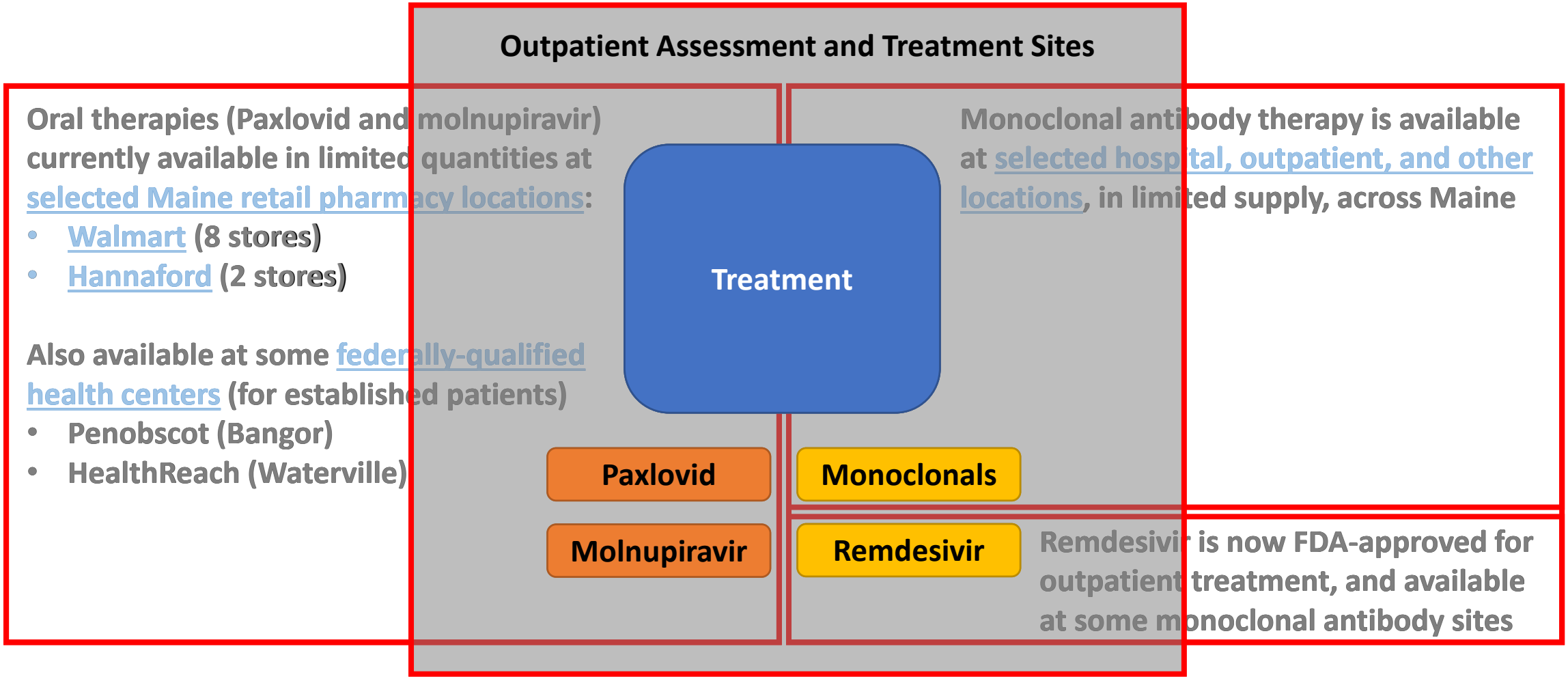
**Paxlovid, sotrovimab, bebtelovimab, and molnupiravir are only available under FDA EUA and must be prescribed in accordance with FDA EUA for individuals diagnosed with COVID-19 and mild/moderate illness at high risk for developing severe disease. Off-label prescribing is not available for drugs that are available under FDA EUA.*

***Remdesivir is FDA-approved for non-hospitalized patients 12 years and older (40 kg and up). It is also available under FDA EUA for patients <12 years old (3.5 to 40 kg).*

Selection Considerations for Clinical Options

Drug category	Drugs available	Considerations
Oral antivirals	**Paxlovid (PO)** **molnupiravir (PO)**	"Strategic niche" for outpatient treatment of COVID-19 similar to that of oseltamivir (Tamiflu) for influenza: prescribe within the first 5 days after symptom onset, possibly without in-person visit; consider molnupiravir for renal impairment, hepatic failure, or certain drug-drug interactions
IV monoclonals	**sotrovimab (IV)** **bebtelovimab (IV)**	Greater acceptance, can be used within 7 days after symptom onset; limited based on need for an infusion site, fewer locations in the state
IV antivirals	**remdesivir (IV)**	IV infusion x3 days that must be covered by patient's own insurance

Treatment options and locations



Coronavirus Disease 2019 (COVID-19)
- COVID-19 Homepage
- Maine Data
- General Information
- Contact Tracing
- Travelers
- Healthcare Providers
- Long Term Care Facilities and Congregate Living
- Communities, Schools, and Workplaces

EPI Information
- A-Z Index of Epidemiology Diseases
- Contact Us
- Disease Reporting
- Request for Data

COVID-19 Treatment in Maine

Who should get treated for COVID-19?

There are now several medications available to treat COVID-19. If you have tested positive for COVID-19, your health care provider might recommend several types of treatment that may relieve symptoms and support your body's natural defenses. If you have tested positive for COVID-19 and are at high risk of severe illness, hospitalization, and death, your health care provider might recommend that you get a specific medication to reduce your chance of more severe illness, hospitalization, and death.

If you have tested positive for COVID-19, are experiencing mild to moderate symptoms, and are at high risk for severe illness, contact your health care provider or one of the COVID-19 Outpatient Assessment and Treatment Sites listed below to review treatment options.

Vaccination remains the best way to prevent COVID-19-related illness, hospitalization, and death. While medicines are highly effective in preventing hospitalization and death, they do not prevent COVID-19 infection and several of these medicines are currently available in only very limited supply across the United States and in Maine.

What COVID-19 treatments are available?

Several medicines are currently available for patients with COVID-19 at high risk of severe illness, including hospitalization or death. Eligibility is set by the U.S. Food and Drug Administration (FDA).

Medicine	Type	Length of treatment	When to start	Who can get this medicine?
Remdesivir	Intravenous (IV)	3 days	Within 0–7 days after COVID-19 symptoms start	Eligible individuals 12+ years old at high risk for progression to severe COVID-19
Sotrovimab (a monoclonal antibody)	Intravenous (IV)	1 day	Within 0–10 days after COVID-19 symptoms start	Eligible individuals 12+ years old at high risk for progression to severe COVID-19
Paxlovid	Oral (by mouth)	5 days	Within 0–5 days after COVID-19 symptoms start	Eligible individuals 12+ years old at high risk for progression to severe COVID-19
Molnupiravir	Oral (by mouth)	5 days	Within 0–5 days after COVID-19 symptoms start	Eligible individuals 18+ years old at high risk for progression to severe COVID-19

https://www.maine.gov/dhhs/mecdc/infectious-disease/epi/airborne/coronavirus/covid19-treatment.shtml

Coronavirus Disease 2019 (COVID-19) - Updates and Information

Coronavirus Disease 2019 (COVID-19)
- COVID-19 Homepage
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211 Get Connected. Get Answers. Social services help

COVID-19: Healthcare Providers

On this page:

Standing Order

On July 1, 2021, Maine CDC issued a revised Standing Order ("Order") that authorizes any health care provider or other trained personnel at a health care facility or medically-supervised COVID-19 collection site (collectively, "collection site") in the state to collect and submit for laboratory analysis specimens to be tested using a SARS-CoV-2 PCR molecular or antigen test for any individual in accordance with the conditions of the Order. Read the Standing Order (PDF).

The Order is not meant to replace existing patient-provider relationships or provider-laboratory relationships.

The Order also authorizes the collection site that submitted the specimen for SARS-CoV-2 molecular or antigen testing under this Order to receive the results of the test directly from the testing laboratory. This Order further authorizes the laboratory that performed the molecular or antigen test for SARS-CoV-2 to provide test results directly to the individual who was tested, with the individual's consent.

https://www.maine.gov/dhhs/mecdc/infectious-disease/epi/airborne/coronavirus/providers.shtml

MaineHealth: remdesivir monitoring

Parameters measured under the definition ‘vital signs’ (VS): Temp, HR, RR, blood pressure, O2 sat

Dose 1:

- VS before infusion
- VS at 15 mins (halfway through 30 min infusion)
- VS at 30 mins (end of infusion)
- VS after 15 min monitoring (prior to discharge)

Total of 4 sets

Dose 2 & 3:

- VS before infusion
- VS at 15 mins (halfway through 30 min infusion)
- VS at 30 mins (end of infusion, this serves as the prior to discharge VS as well)

Total of 3 sets

Key resources

- Maine CDC: COVID-19 provider information (https://www.maine.gov/dhhs/mecdc/infectious-disease/epi/airborne/coronavirus/providers.shtml)
- Maine CDC: COVID-19 Treatment in Maine **(information for patients)** (https://www.maine.gov/dhhs/mecdc/infectious-disease/epi/airborne/coronavirus/covid19-treatment.shtml)
- Maine CDC: Health Advisories (https://www.maine.gov/dhhs/mecdc/newhan.shtml)
- NIH: Coronavirus Disease 2019 (COVID-19) Treatment Guidelines (https://www.covid19treatmentguidelines.nih.gov)
- ASPR: COVID-19 Therapeutics (https://aspr.hhs.gov/COVID-19/Therapeutics)

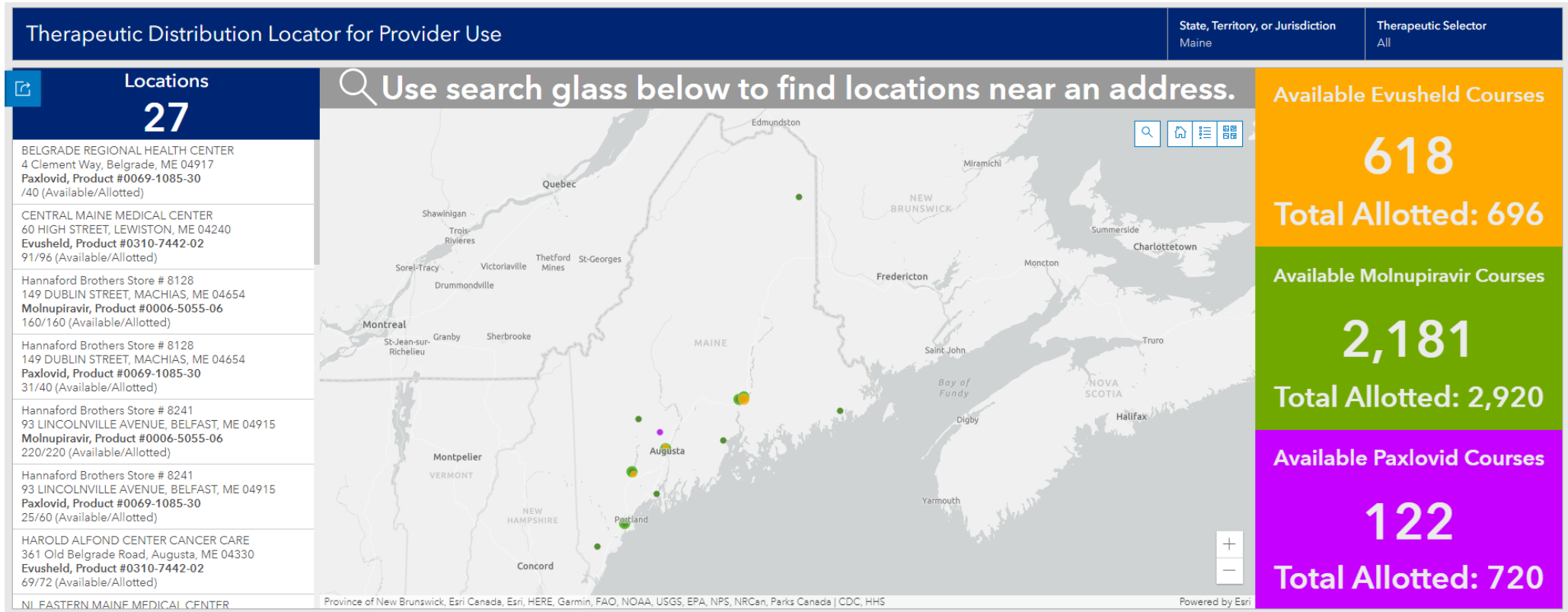
Department of Health and Human Services (HHS) COVID-19 Therapeutics Locator

COVID-19 Therapeutics Locator

The national map below displays public locations that have received shipments of U.S. Government-procured COVID-19 therapeutics under U.S. Food and Drug Administration (FDA) Emergency Use Authorization (EUA) authority. The locations displayed in the locator have reported stock on hand within the last day.

The monoclonal antibody treatment Evusheld (Astra Zeneca), as well as the oral antiviral therapies Paxlovid (Pfizer), and molnupiravir (Merck) are products authorized by the FDA for either prevention (Evusheld) or treatment (Paxlovid and molnupiravir) of COVID-19.

These therapies require a prescription by a licensed and authorized provider. Patients should coordinate with their healthcare provider prior to contacting a location to receive these therapies.



https://covid-19-therapeutics-locator-dhhs.hub.arcgis.com/

Additional COVID Resources

- Coronavirus Disease 2019 (COVID-19) | US CDC
- US CDC COVID-19 Vaccines Clinical Considerations
- Maine COVID-19 Vaccines (maine.gov)
- Maine COVID-19 Vaccines FAQ
- Maine COVID-19 Vaccination Sites
- HHS/ASPR Website (mAbs): www.phe.gov/mAbs
- HHS Website (mAbs): https://combatcovid.hhs.gov/
- FDA Paxlovid EUA Health Care Provider Fact Sheet
- FDA Molnupiravir EUA Health Care Provider Fact Sheet

Current Authorized/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
  - nirmatrelvir and ritonavir (Paxlovid™)
    - 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
  - sotrovimab
    - sotrovimab provider fact sheet: https://www.fda.gov/media/149534/download
    - sotrovimab patient fact sheet: https://www.fda.gov/media/149533/download
    - sotrovimab patient fact sheet (Spanish): https://www.fda.gov/media/154376/download
  - 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

Current Authorized/Approved COVID-19 Outpatient Therapeutics (cont'd)

- 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
  - remdesivir (Veklury®)
    - Veklury (remdesivir) Prescribing Information: https://www.vekluryhcp.com/
    - remdesivir provider fact sheet: https://www.fda.gov/media/137566/download
    - remdesivir patient fact sheet: https://www.fda.gov/media/137565/download
    - remdesivir patient fact sheet (Spanish): https://www.fda.gov/media/139460/download
  - molnupiravir
    - molnupiravir provider fact sheet: https://www.fda.gov/media/155054/download
    - molnupiravir patient fact sheet: https://www.fda.gov/media/155055/download
    - molnupiravir patient fact sheet (Spanish): https://www.fda.gov/media/155115/download
  - tixagevimab and cilgavimab (EVUSHELD™)
    - 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