COVID-19 Outpatient Treatment in Maine:
A Primer for Prescribers

July 20, 2022

STATE OF MAINE
Department of
Health and Human Services

COVENANT HEALTH

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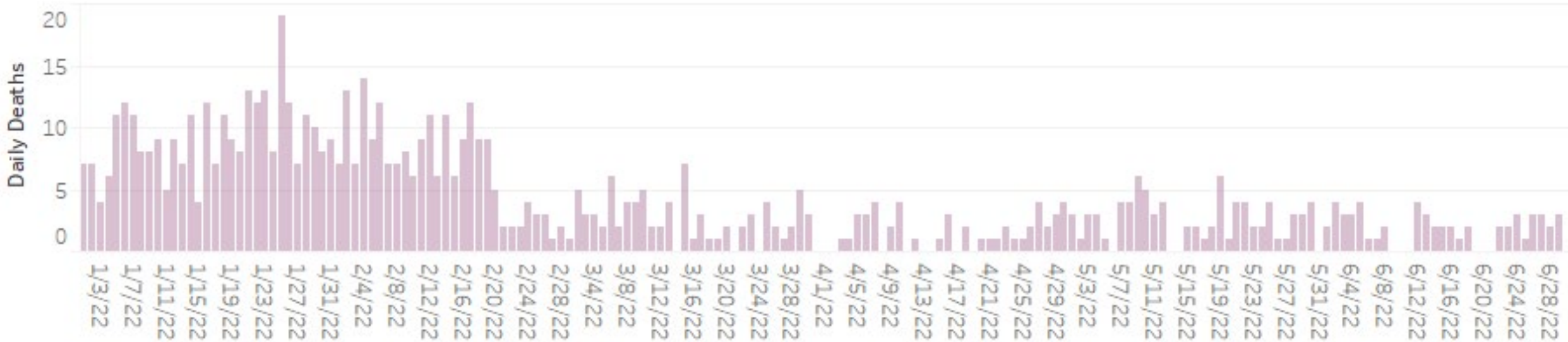
Section	Video Link
COVID-19 Treatment in Maine: A Primer for Prescribers	https://youtu.be/gT9kGMcN9iw
Oral and Intravenous Medications for COVID-19	https://youtu.be/O-9LScCBX08
Accessing COVID-19 Therapeutics: Community Access & Resources	https://youtu.be/-OF-hjrrj64
Mild COVID in a 65-year-old Male	https://youtu.be/wGw8h_jSI90
Positive Test and No COVID Symptoms	https://youtu.be/MfEjEm_cAVE
Mild COVID in a 47-year-old Male	https://youtu.be/sdg4KUS9bJM
Hospitalized Patient with a Positive COVID-19 Screening Test	https://youtu.be/vKuNgRVwnP4
Pregnancy and COVID-19	https://youtu.be/e1RtTyIaedA
Pediatric COVID-19 Treatment	https://youtu.be/J4HIV7KsRdM
Addressing Renal Function when Prescribing Paxlovid	https://youtu.be/_qtUddesKrk
Specific Drug-Drug Interactions with Paxlovid: Anticoagulants	https://youtu.be/TWM-5iHzmMw
Managing Paxlovid Drug-Drug Interactions	https://youtu.be/tOdIwEl--Gw
Severe COVID-19	https://youtu.be/wPTrV25B5LQ
Lagevrio Use Case Scenario	https://youtu.be/gdriUhZCP_8

Why are people still dying from COVID-19?



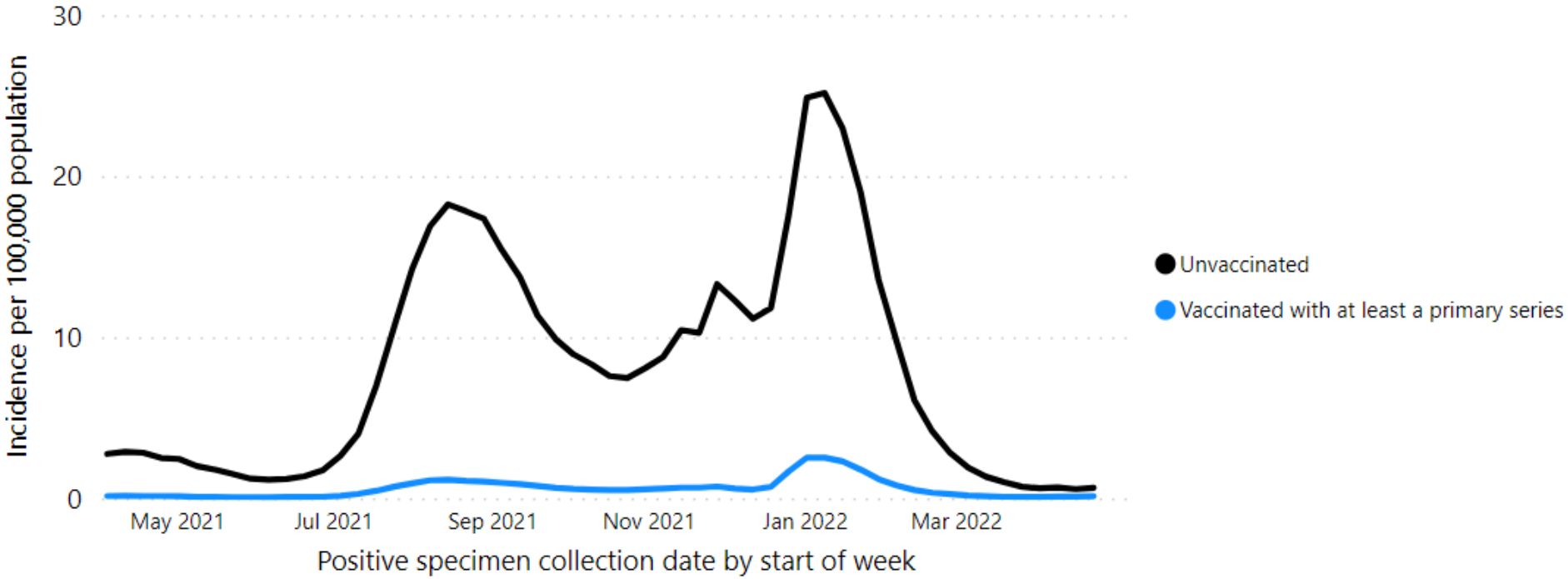
Risk for COVID-19 Infection, Hospitalization, and Death by Age Group

Rate compared to 18-29 years old	0-4 years old	5-17 years old	18-29 years old	30-39 years old	40-49 years old	50-64 years old	65-74 years old	75-84 years old	85+ years old
Cases	<1x	1x	Reference group	1x	1x	1x	1x	1x	1x
Hospitalization	1x	<1x	Reference group	2x	2x	3x	5x	8x	10x
Death	<1x	<1x	Reference group	4x	10x	25x	65x	140x	330x

https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-age.html

Rates of COVID-19 Deaths by Vaccination Status in Ages 5+ Years

April 04, 2021–April 30, 2022 (30 U.S. jurisdictions)



Unvaccinated people aged 5 years and older had:

1.9X
Risk of Testing Positive for COVID-19

AND

6X
Risk of Dying from COVID-19

in April 2022, and

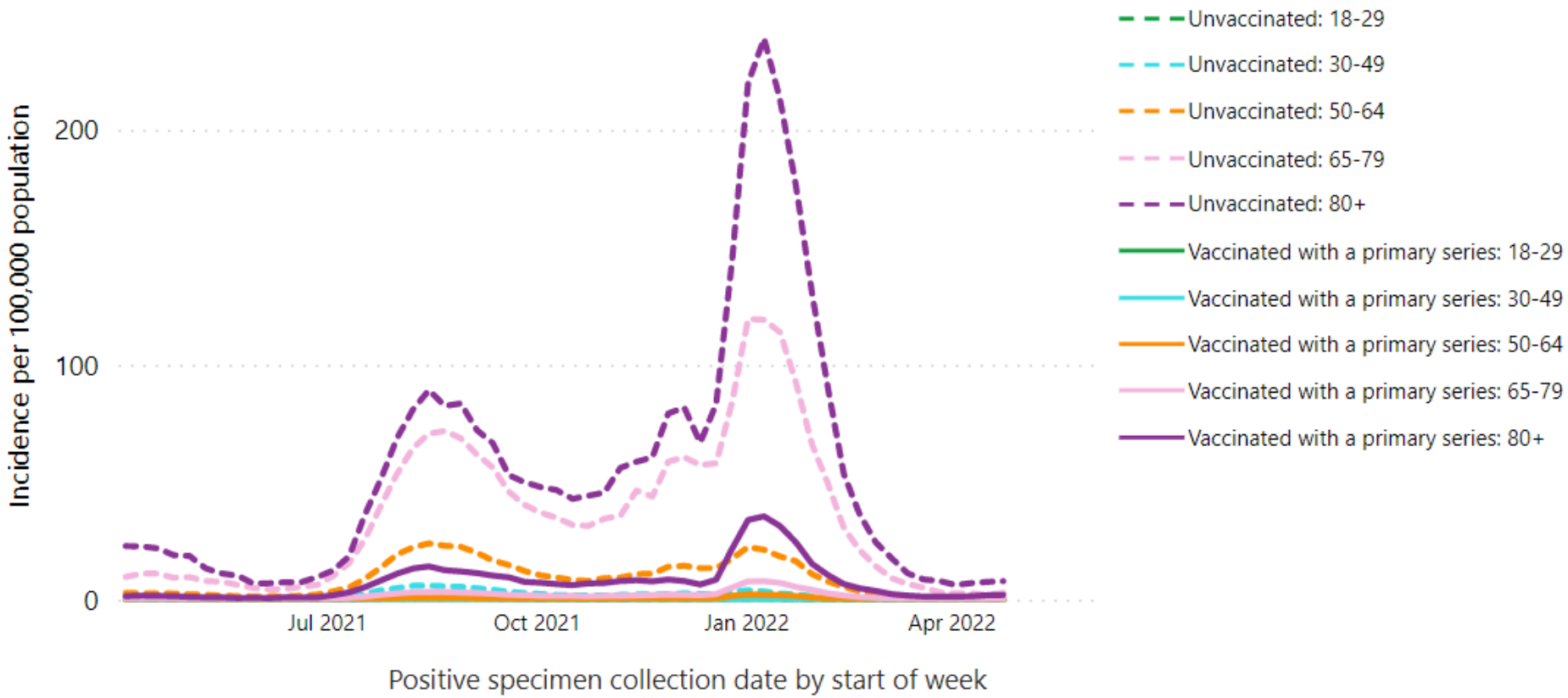
2.0X
Risk of Testing Positive for COVID-19

in May 2022,* compared to people vaccinated with at least a primary series.

Source: CDC COVID-19 Response, Epidemiology Task Force, Surveillance & Analytics Team, Vaccine Breakthrough Unit

Rates of COVID-19 Deaths by Vaccination Status and Age Group

April 04, 2021–April 30, 2022 (30 U.S. jurisdictions)



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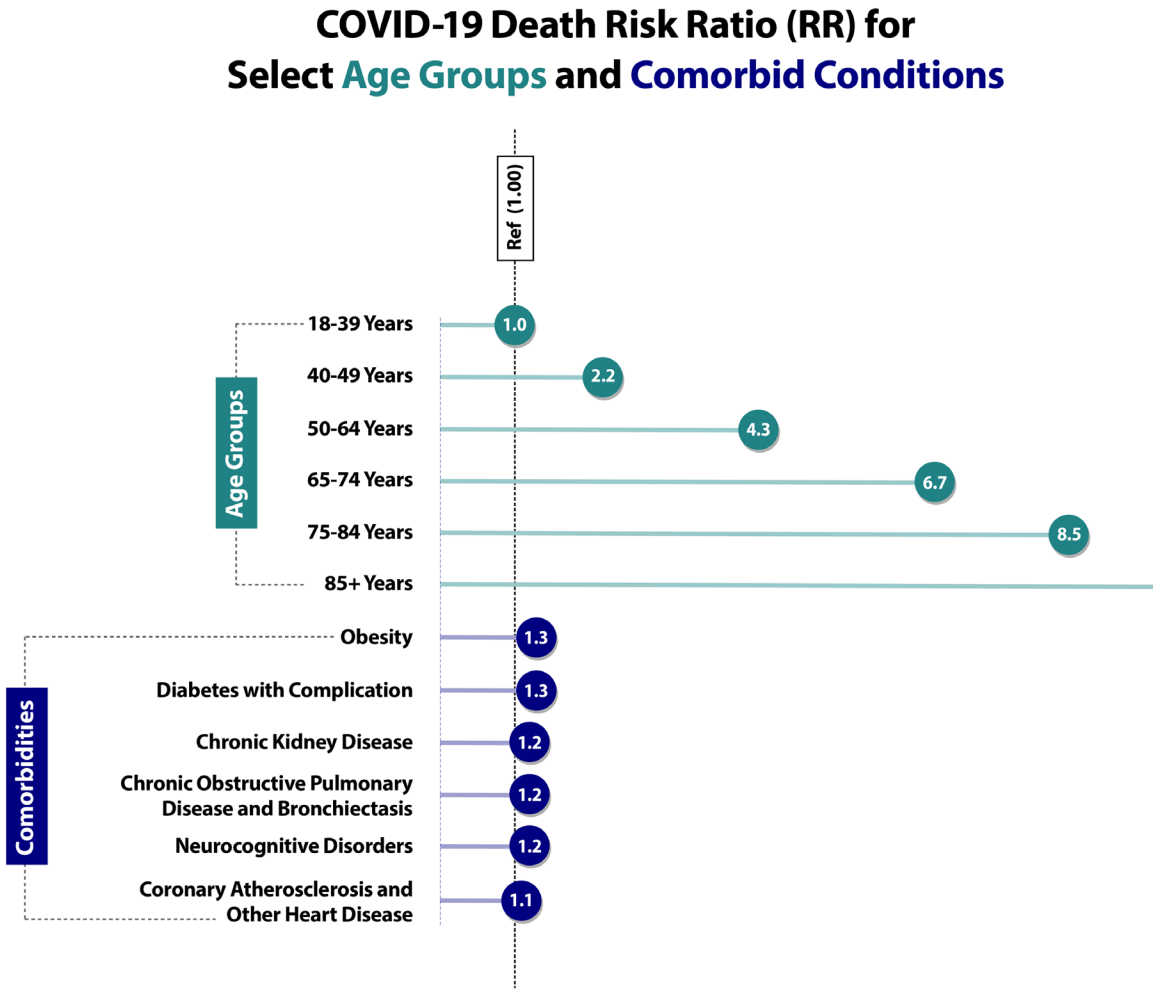
Source: CDC COVID-19 Response, Epidemiology Task Force, Surveillance & Analytics Team, Vaccine Breakthrough Unit

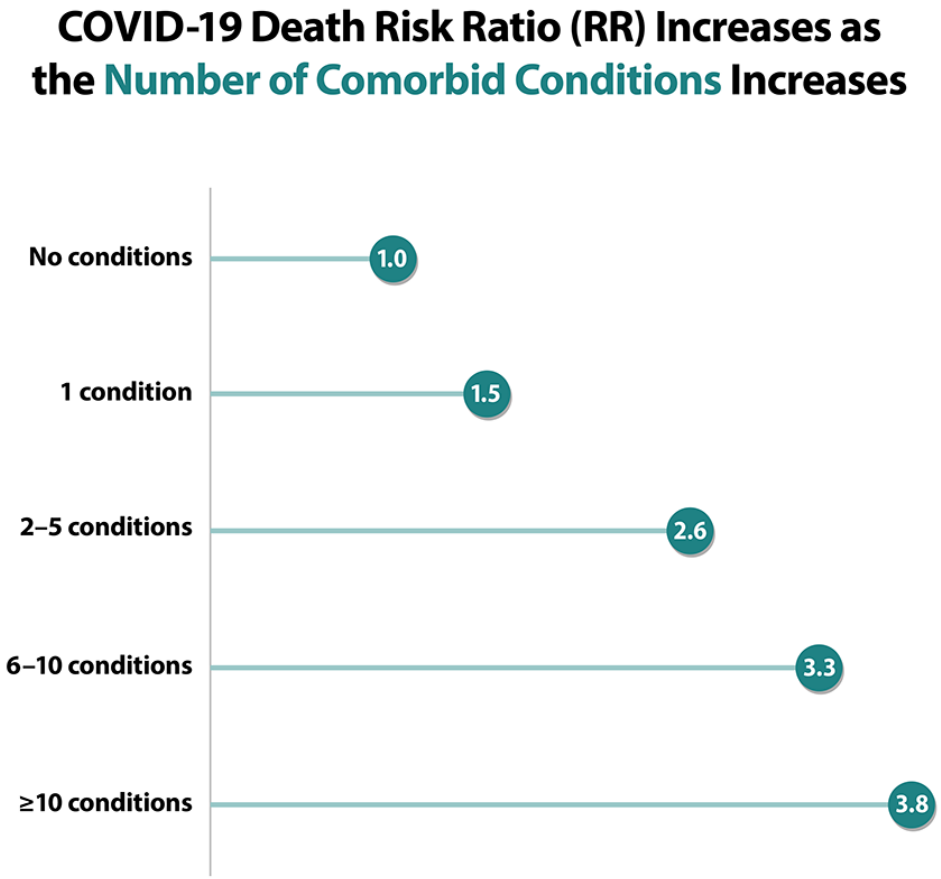
Conditions that increase risk of severe disease

- 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
- 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) and *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)

Risk goes up with age, multiple comorbidities





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)

Treatment of Non-Hospitalized Patients with Mild-Moderate COVID-19 at High Risk of Disease Progression

- A number of therapeutics are authorized or approved for the treatment of mild-to-moderate COVID-19 in adults and certain pediatric patients 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.
- Primary care physicians can play a key role utilizing these therapeutics to help reduce the risk of hospitalization or death in high-risk patients with mild-moderate COVID-19.

CDC: Interim Clinical Considerations for COVID-19 Treatment in Outpatients

What You Need to Know:

- There is strong scientific evidence that antiviral treatment of outpatients at risk for severe COVID-19 reduces their risk of hospitalization and death.

- The antiviral drugs **Paxlovid (ritonavir-boosted nirmatrelvir)** and **Veklury (remdesivir)** are the preferred treatments for eligible adult and pediatric patients with positive results of direct SARS-CoV- 2 viral testing and who are at high risk for progression to severe COVID-19.

- Clinicians should consider COVID-19 treatment in non-hospitalized patients who meet all of the following:
  - Test positive for SARS-CoV-2 (with PCR or antigen test, including at-home tests)
  - Have symptoms consistent with mild-to-moderate COVID-19. People with mild COVID-19 experience symptoms such as fever, sore throat, cough, or headache that do not affect the lungs and breathing. People with moderate illness have symptoms that affect the lungs like shortness of breath or difficulty breathing.
  - Are within 5 days of symptom onset for Paxlovid or 7 days of symptom onset for Veklury
  - Have one or more risk factors for severe COVID-19

See: Interim Clinical Considerations for Covid-19 Treatment in Outpatients
https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/outpatient-treatment-overview.html

CDC: Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19

Risk factors for severe COVID-19 include:

- Age over 50 years, with risk increasing substantially at age ≥ 65 years
- Being unvaccinated or not being up to date on COVID-19 vaccinations
- Specific medical conditions and behaviors

Some people from racial and ethnic minority groups are at risk of being disproportionately affected by COVID-19 from many factors, including limited access to vaccines and healthcare. Healthcare providers can consider these factors when evaluating the risk for severe COVID-19 and use of outpatient therapeutics.

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

Direct SARS-CoV-2 Viral Testing

- Two types of diagnostic tests:
  - Molecular tests, such as PCR tests, that detect the virus's genetic material
  - Rapid antigen diagnostic tests that detect specific proteins from the virus
- Patients in the authorized population who report a positive home test result from a rapid antigen diagnostic test to their provider are eligible for the therapeutic.
- A positive PCR also meets the requirement.
- Confirmation of a positive home rapid antigen diagnostic test with additional testing, such as a PCR, is not required.

Summary of COVID-19 Preventative Agents & Therapeutics

No Illness	Exposed Per CDC Close Contact Criteria	Mild to Moderate Symptoms	Hospital Admission			ICU Admission	
Baseline health status, no infection	Not hospitalized, no limitations	Not hospitalized, with limitations[1]	Hosp. no act. medical problems	Hospitalized, not on oxygen	Hospitalized, on oxygen	Hospitalized, high flow oxygen/ non-invasive ventilation	Hospitalized, mechanical ventilation/ ECMO

Veklury® (remdesivir, Gilead) and
Paxlovid (nirmatrelvir + ritonavir, Pfizer) - **Preferred**

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**

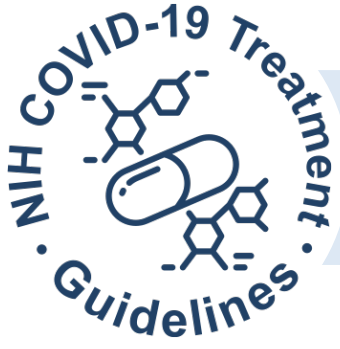
Please see NIH Current Inpatient Therapies
(https://www.covid19treatmentguidelines.nih.gov/therapies/)

[1] Therapeutic Management of Nonhospitalized Adults With COVID-19 https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults--therapeutic-management/
[2] Therapeutic Management of Hospitalized Adults With COVID-19 https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/hospitalized-adults--therapeutic-management/

NIH COVID-19 Treatment Guidelines

- The COVID-19 Treatment Guidelines Panel (the Panel) has recommended several therapeutic agents for the treatment and prevention of SARS-CoV-2 infection in individuals who are at high risk for progression to severe COVID-19.

- These anti-SARS-CoV-2 therapeutics are of greatest benefit for non-hospitalized patients who have risk factors for progression to severe COVID-19. The risks for progression are substantially higher for those who are not vaccinated or who are vaccinated but not expected to mount an adequate immune response to the vaccine.



Please see the NIH COVID-19 Treatment Guidelines for more information.
(https://www.covid19treatmentguidelines.nih.gov/therapies/)

Figure 1. Therapeutic Management of Nonhospitalized Adults With COVID-19

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Does Not Require Hospitalization or Supplemental Oxygen	All patients should be offered symptomatic management **(AIII)**. For patients who are at high risk of progressing to severe COVID-19,[a] use 1 of the following treatment options: **Preferred Therapies** *Listed in order of preference:* • **Ritonavir-boosted nirmatrelvir (Paxlovid)[b,c] (AIIa)** • **Remdesivir[c,d] (BIIa)** **Alternative Therapies** *For use ONLY when neither of the preferred therapies are available, feasible to use, or clinically appropriate. Listed in alphabetical order:* • **Bebtelovimab[e] (CIII)** • **Molnupiravir[c,f] (CIIa)** The Panel **recommends against** the use of **dexamethasone[g]** or **other systemic corticosteroids** in the absence of another indication **(AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Weak
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Summary of COVID-19 Vaccines and Therapeutics

Category or Population	What's Available?	Resources and Notes
Age 6 months and older	• COVID-19 vaccines • COVID-19 boosters	• US CDC: Use of COVID-19 Vaccines in the United States • Maine CDC: COVID-19 Vaccine Providers Portal
Age 6 months and older with moderate or severe immunocompromise	• COVID-19 vaccines • COVID-19 boosters • Long-acting antibody for pre-exposure prophylaxis	• US CDC: COVID-19 Vaccines for People who are Moderately or Severely Immunocompromised • Maine CDC: COVID-19 Vaccine Providers Portal • COVID-19 Pre-Exposure Prophylaxis (Provider Information)
Exposed to COVID-19 who have not tested positive (i.e., post-exposure prophylaxis)	• **No** treatments available	• All monoclonal antibodies previously available for post-exposure prophylaxis are not effectiveness for current COVID-19 variants.
Asymptomatic COVID-19 infection	• Symptomatic treatment	• Monitor for development of COVID-19 symptoms and treat if high-risk. • Ensure readiness to test and access treatment quickly if eligible and symptomatic.
Mild/moderate COVID-19 symptoms and positive test but NOT at elevated risk for COVID-19 severe disease based on age, vaccination, or other high-risk condition	• Symptomatic treatment	
Persons with mild/moderate COVID-19 illness **PLUS positive test** **PLUS:** • **age 50 years or older OR** • **unvaccinated OR** • **have one or more underlying condition that places them at high risk for severe disease**	• Oral antivirals • IV antivirals • IV monoclonal antibodies	• For information on pharmacies that can fill a prescription, and information on Test-to-Treat locations where patients can get tested, seen by a clinician, and treated with oral or intravenous COVID-19 therapies, see COVID-19 Treatment in Maine.

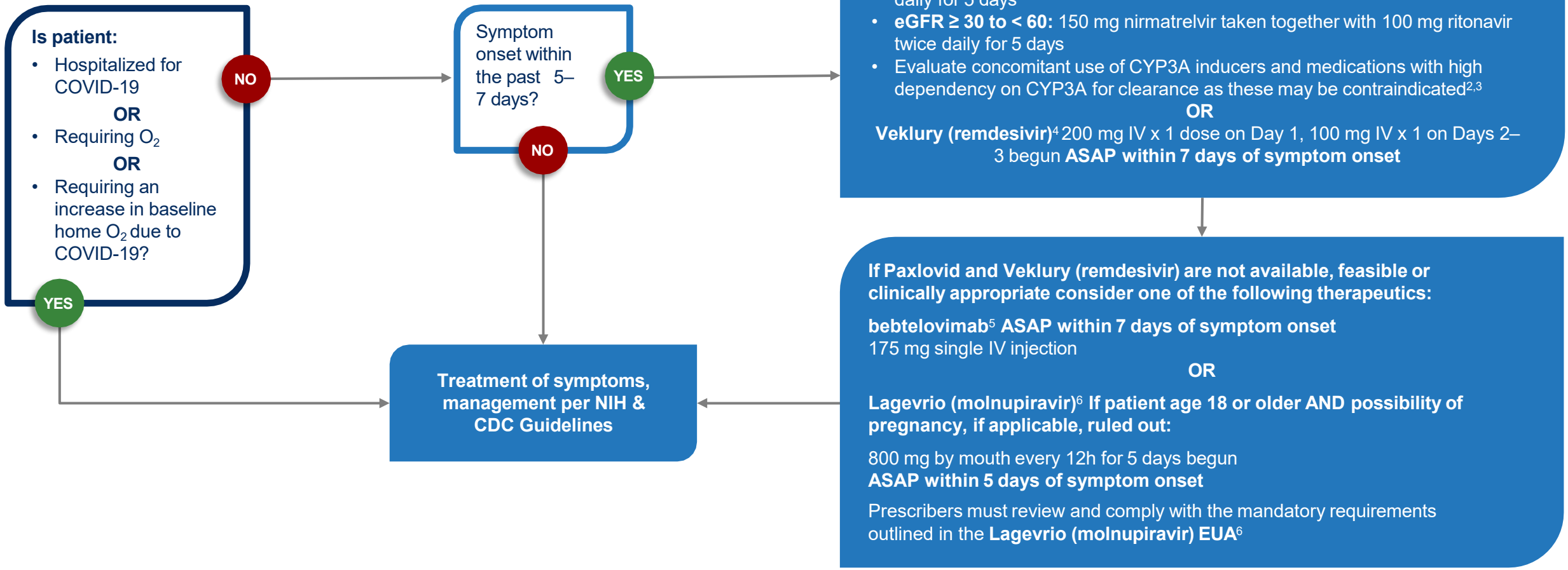
COVID-19 Outpatient Therapy Selection

Drug/route	Key features	Eligible population	Key considerations for use
Paxlovid (nirmatrelvir/ ritonavir) (PO)	• Oral (5 days) • Start within 0–5 days after COVID-19 symptoms begin	**Individuals 12+ years old at high risk for progression to severe COVID-19**	• Treatment of choice for non-hospitalized patients (per NIH guidelines). • Providers should check for drug-drug interactions and make medication changes that can be accomplished safely. Renal dosing adjustment is needed for patients with GFR between 30–60. • Do not use for severe renal impairment (GFR <30) or severe hepatic impairment (Child-Pugh C).
Veklury (remdesivir) (IV)	• Intravenous (once-daily therapy for 3 days) • Start within 0–7 days after COVID-19 symptoms begin	**Individuals 28 days old and older at high risk for progression to severe COVID-19**	• 2nd-line treatment option per NIH treatment guidelines. This is the best option for patients who cannot take Paxlovid due to drug-drug interactions. • Requires insurance coverage and multiple days of IV infusion. Currently only available at a few facilities, and primarily for outpatients under 12 years old. • Consider for eligible patients who are hospitalized for a non-COVID-19 cause if Paxlovid is not available in inpatient formulary or oral access is unavailable.
Bebtelovimab (IV)	• Intravenous (1 dose) • Start within 0–7 days after COVID-19 symptoms begin	**Individuals 12 years old and older at high risk for progression to severe COVID-19**	• Best pick for patients presenting between 6–7 days after symptom onset (outside the Paxlovid treatment window) or who cannot take oral drugs for any reason. • Also the best pick for patients unable to get Paxlovid due to drug-drug interaction that can't be addressed safely, severe kidney or liver disease, or concerns about the patient's ability to complete 5 days of outpatient therapy.
Lagevrio (molnupiravir) (PO)	• Oral (5 days) • Start within 0–5 days after COVID-19 symptoms begin	**Individuals 18 years old and older at high risk for progression to severe COVID-19**	• Best pick for patients who cannot get Paxlovid due to drug-drug interaction or severe kidney or liver disease, and who do NOT have access to IV therapy. • Lower effectiveness than the other three therapies. • Avoid in pregnancy if other treatment options are available.

COVID-19 Outpatient Therapeutics

Clinical Decision Aid for Ages 12+

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



References:

[1] NIH's COVID-19 Treatment Guidelines Therapeutic Management of Nonhospitalized Adults With 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: Ritonavir-Boosted Nirmatrelvir (Paxlovid). https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/

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

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

[6] Lagevrio EUA. https://www.fda.gov/media/155054/download

ASPR
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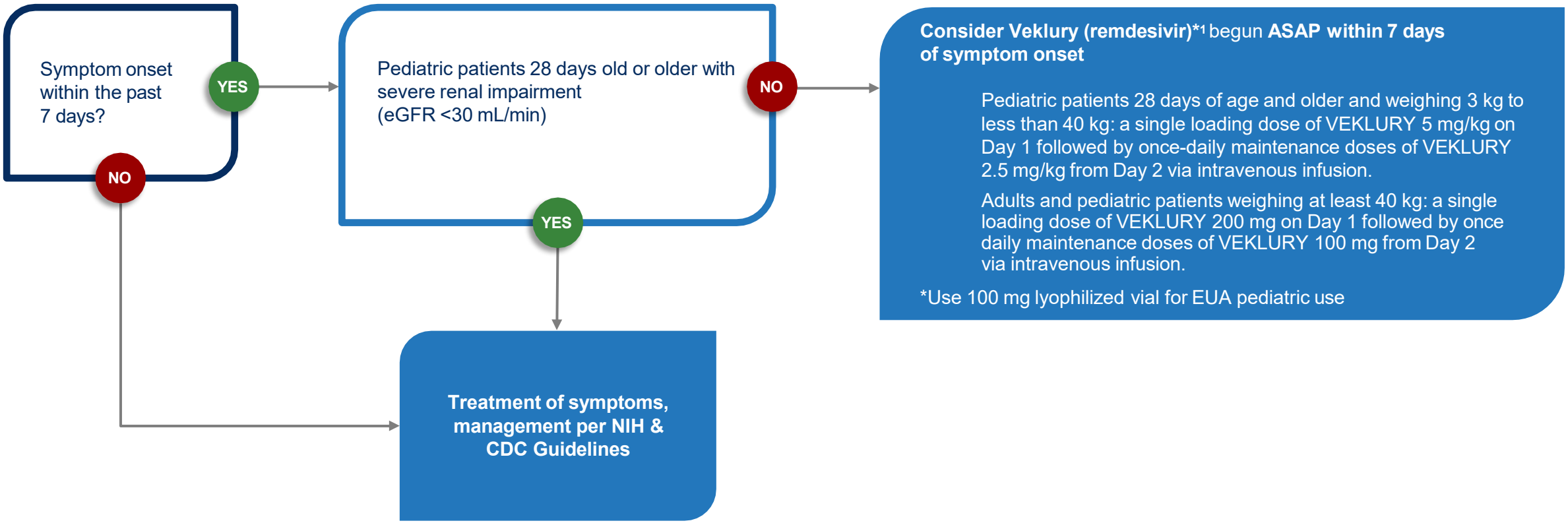
April 18, 2022

Clinical Decision Aid for Pediatric Patients

Outpatient **Pediatric patients 28 days of age and older weighing at least 3 kg**, with mild to moderate COVID-19 and at high risk for progression to severe disease



Reference:

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

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ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

Drug	Dosing	Duration	Time from Symptom Onset	Specific issues
Nirmatrelvir (N) + ritonavir (RTV)	eGFR ≥60mL/min: N 300 mg with RTV 100 gm po bid eGFR ≥30 to <60 mL/min Nirmatrelvir 150 mg with RTV 100 mg po bid	5 days	≤5 days	• DDIs • Not recommended with Child-Pugh Class C
Remdesivir (RDV)	RDV 200 mg IV F/B 100 mg IV daily	Day 1 Day 2, 3	≤ 7 days	• Infusion over 30-120 min • Infusions over 3 consecutive days
Bebtelovimab (BEB)	BEB 175 mg IV	Day 1	≤ 7 days	• Administer ≥30 seconds • No clinical endpoint data
Molnupiravir (MOL)	MOL 800 mg po bid	5 days	≤5 days	• Potentially less efficacious than other options • Safety concerns

Why don’t patients get treated early in illness?

- **Healthcare providers lack…**
  - Knowledge about who should be treated
  - Knowledge about how to access treatment

- **High-risk patients lack…**
  - Knowledge that treatment is available
  - Knowledge that treatment works well
  - Knowledge of who should get treated
  - Knowledge of how to access treatment
  - Ability to get tested early in illness
  - Ability to see healthcare provider rapidly after getting positive test result
  - Ability to access pharmacies, hospitals, and clinics with treatments

What can providers do to help their patients?

Key messages for healthcare providers:

- Become familiar with COVID-19 treatments for outpatients
- Talk to your high-risk patients about the value of treatment
- Encourage high-risk patients to have a plan to get tested and treated before they get sick

Key messages for high-risk patients:

- COVID-19 treatments are safe, effective, and drastically reduce the risk of severe disease
- Treatment must be started within the first few days after symptom onset to be effective
- Have a plan to get tested, evaluated, and treated if you develop symptoms of COVID-19

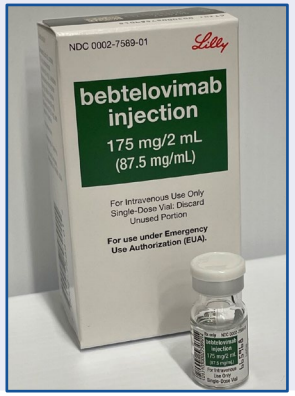
Key resources

- **Maine CDC: COVID-19 provider information**
  https://www.maine.gov/dhhs/mecdc/infectious-disease/epi/airborne/coronavirus/providers.shtml
- **COVID-19 Vaccines and Therapeutics** (Provider Information)
  https://www.maine.gov/dhhs/mecdc/infectious-disease/epi/airborne/coronavirus/covid19-treatment.shtml
- **Maine CDC: COVID-19 Treatment in Maine** (Patient Information)
  https://www.maine.gov/covid19/treatment
- **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

Oral and Intravenous Medications for COVID-19

Isaac Benowitz, MD
State Epidemiologist
Maine CDC

Overview of COVID-19 Outpatient Therapy

Class	Oral	Intravenous
Antivirals	Paxlovid   Lagevrio	remdesivir 
Monoclonal antibodies		 bebtelovimab

COVID-19 Outpatient Therapy Summary

Drug name	Paxlovid (ritonavir/nirmatrelvir)	Veklury (remdesivir)	Bebtelovimab (monoclonal antibody)	Lagevrio (molnupiravir)
Effectiveness	88%	87%	Unknown	30%
Age allowed for use	≥ 12 years	≥ 28 days	≥ 12 years	≥ 18 years
Initiate within # days of symptom onset	0–5 days	0–7 days	0–7 days	0–5 days
Route of administration	Oral	Intravenous	Intravenous	Oral
Duration of treatment	5 days	3 days	1 day	5 days
Pros	• High efficacy • Oral	• High efficacy • Greater experience	• High efficacy • Single IV infusion	• Oral • No drug-drug interaction concerns
Cons	• Ritonavir-related drug-drug interactions	• Requires 3 days of IV infusion	• Requires IV infusion	• Low efficacy • Not authorized for age <18y • Avoid in pregnancy • Mutagenicity concerns

Paxlovid

Paxlovid (nirmatrelvir and ritonavir) – Pfizer *Oral Antiviral*

Standard

Renal

[Paxlovid Product Information]

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

For more information, Fact Sheet for Healthcare Providers for Paxlovid (nirmatrelvir and ritonavir)

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

For more information, Fact Sheet for Healthcare Providers for Paxlovid (nirmatrelvir and ritonavir)

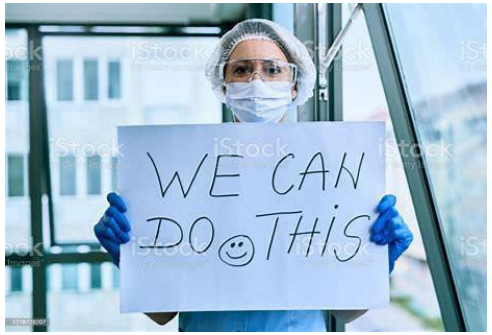
Paxlovid

Paxlovid contains Nirmatrelvir (a SARS-CoV-2 main protease inhibitor (aka Mpro, 3CLpro, or nsp5)) and Ritonavir (a strong CYP3A inhibitor included as a pharmacokinetic enhancer to increase nirmatrelvir plasma levels)

- Regulatory Status: Emergency Use Authorization
- Age Range: adults and pediatric patients (12 years of age and weighing at least 40 kg)
- Dosing: (standard) two 150 mg tablets (300 mg) nirmatrelvir with one 100 mg tablet ritonavir orally bid x 5 days (without regard to food)

Paxlovid

- Timing: as soon as possible after COVID-19 diagnosis and within 5 days of symptom onset
- Special Consideration – Renal Impairment: For patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), the dosage of Paxlovid is 150 mg nirmatrelvir and 100 mg ritonavir for 5 days (special packaging now available). Not recommended for patients with severe renal impairment (eGFR <30 mL/min).
- Special Consideration – Hepatic Impairment: Not recommended for patients with Child-Pugh Class C.
- Special Consideration – Potential Drug Interactions



Paxlovid

- Potential to affect other drugs (ritonavir is a strong CYP3A inhibitor) and for other drugs to affect Paxlovid (components are CYP3A substrates)
- Drug Interaction Resources for Providers:
  - EUA Webpage https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs
    - Fact Sheet for Health Care Providers, Checklist, and more
  - NIH COVID-19 Treatment Guidelines

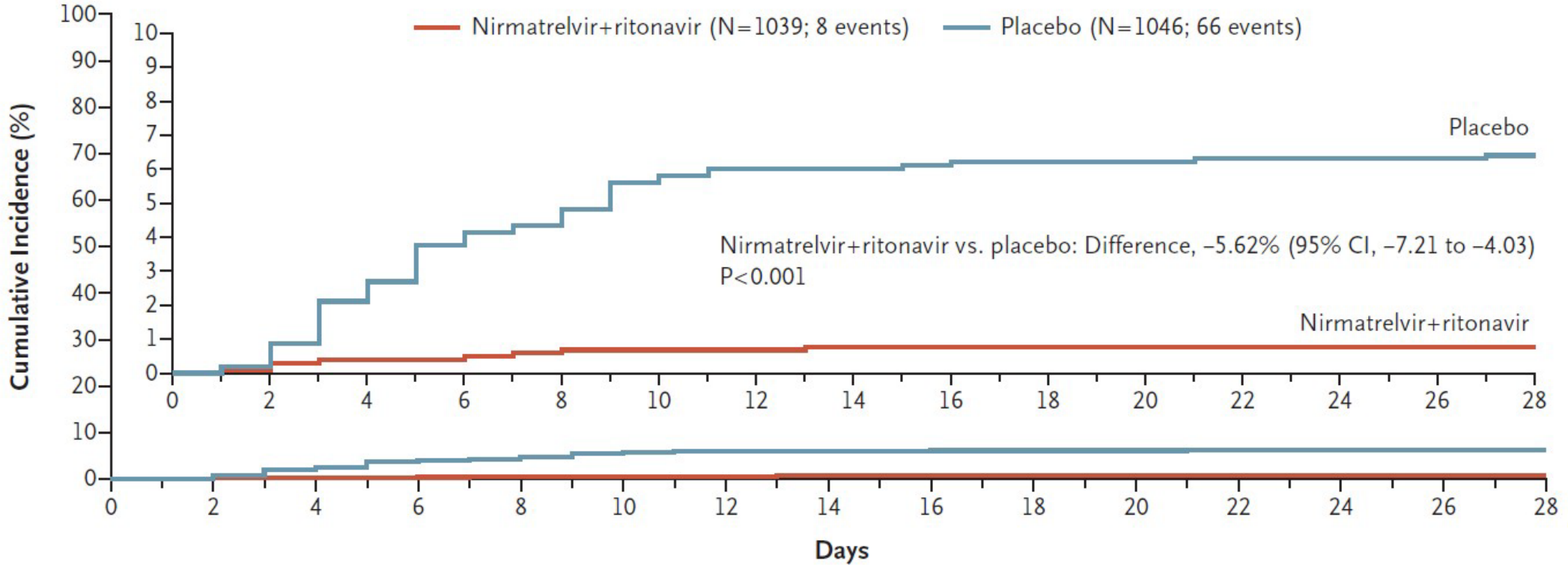
https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/

  - University of Liverpool COVID-19 Drug Interactions

https://www.covid19-druginteractions.org/checker

Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

B **Covid-19–Related Hospitalization or Death from Any Cause through Day 28 among Patients Treated ≤5 Days after Symptom Onset**



No. at Risk

NMV-r	1039	1034	1023	1013	1007	1004	1002	1000	997	995	993	993	993	993	992
Placebo	1046	1042	1015	990	977	963	959	959	955	953	951	948	948	948	945

DOI: 10.1056/NEJMoa2118542

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

Paxlovid (nirmatrelvir and ritonavir) Patient Eligibility Screening Checklist Tool for Prescribers (continued)

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.

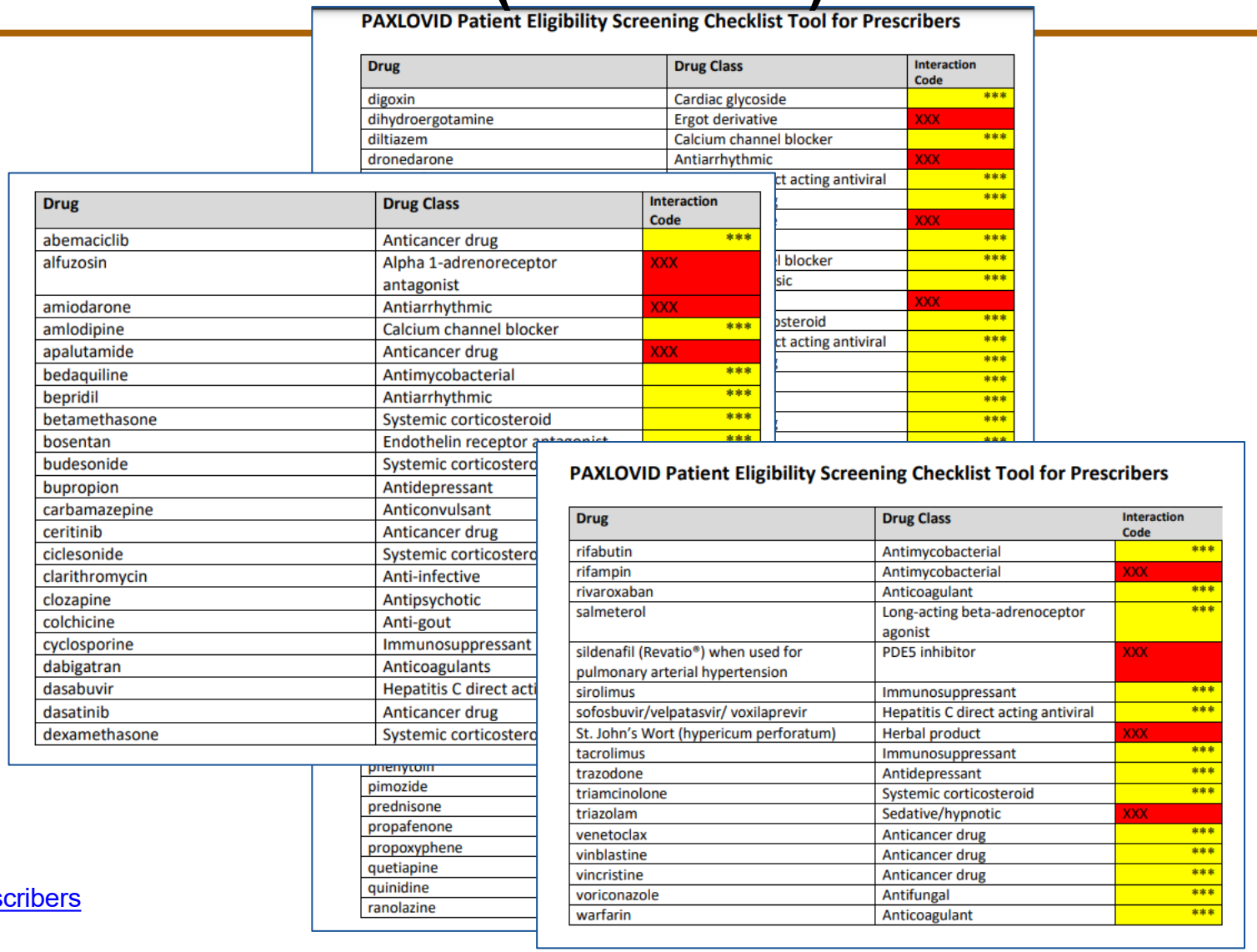
Paxlovid (nirmatrelvir and ritonavir) Patient Eligibility Screening Checklist Tool for Prescribers (continued)

PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers

Other Drugs with Established and Other Potentially Significant Drug Interactions with PAXLOVID (listed alphabetically by generic name)

Interaction Codes:

XXX	Coadministration of this drug with PAXLOVID is CONTRAINDICATED. For further information, refer to the Fact Sheet for Healthcare Providers and the individual Prescribing Information for the drug.
***	Coadministration of this drug with PAXLOVID should be avoided and/or holding of this drug, dose adjustment of this drug, or special monitoring is necessary. Consultation with the prescriber of the potentially interacting drug is recommended. For further information, refer to the Health Care Provider Fact Sheet and the individual Prescribing Information for the drug.



PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers

Drug	Drug Class	Interaction Code
digoxin	Cardiac glycoside	***
dihydroergotamine	Ergot derivative	XXX
diltiazem	Calcium channel blocker	***
dronedarone	Antiarrhythmic	XXX
	ct acting antiviral	***
		***
		XXX
		***
	l blocker	***
	sic	***
		XXX
	osteroid	***
	ct acting antiviral	***
		***
		***
		***
		***
		***
phenytoin		
pimozide		
prednisone		
propafenone		
propoxyphene		
quetiapine		
quinidine		
ranolazine		

PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers

Drug	Drug Class	Interaction Code
abemaciclib	Anticancer drug	***
alfuzosin	Alpha 1-adrenoreceptor antagonist	XXX
amiodarone	Antiarrhythmic	XXX
amlodipine	Calcium channel blocker	***
apalutamide	Anticancer drug	XXX
bedaquiline	Antimycobacterial	***
bepridil	Antiarrhythmic	***
betamethasone	Systemic corticosteroid	***
bosentan	Endothelin receptor a	***
budesonide	Systemic corticosterc	
bupropion	Antidepressant	
carbamazepine	Anticonvulsant	
ceritinib	Anticancer drug	
ciclesonide	Systemic corticosterc	
clarithromycin	Anti-infective	
clozapine	Antipsychotic	
colchicine	Anti-gout	
cyclosporine	Immunosuppressant	
dabigatran	Anticoagulants	
dasabuvir	Hepatitis C direct acti	
dasatinib	Anticancer drug	
dexamethasone	Systemic corticosterc	

PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers

Drug	Drug Class	Interaction Code
rifabutin	Antimycobacterial	***
rifampin	Antimycobacterial	XXX
rivaroxaban	Anticoagulant	***
salmeterol	Long-acting beta-adrenoceptor agonist	***
sildenafil (Revatio®) when used for pulmonary arterial hypertension	PDE5 inhibitor	XXX
sirolimus	Immunosuppressant	***
sofosbuvir/velpatasvir/ voxilaprevir	Hepatitis C direct acting antiviral	***
St. John's Wort (hypericum perforatum)	Herbal product	XXX
tacrolimus	Immunosuppressant	***
trazodone	Antidepressant	***
triamcinolone	Systemic corticosteroid	***
triazolam	Sedative/hypnotic	XXX
venetoclax	Anticancer drug	***
vinblastine	Anticancer drug	***
vincristine	Anticancer drug	***
voriconazole	Antifungal	***
warfarin	Anticoagulant	***

See table in Paxlovid Patient Eligibility Screening Checklist Tool for Prescribers

Paxlovid (nirmatrelvir and ritonavir) Formulation and Packaging

FDA has 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.

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.

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.

*Standard Dose pack may be adapted for renal dosing. See instructions on next slide.

Paxlovid (nirmatrelvir and ritonavir)
Renal Adjustment Instructions for Pharmacists for Standard Dose Pack

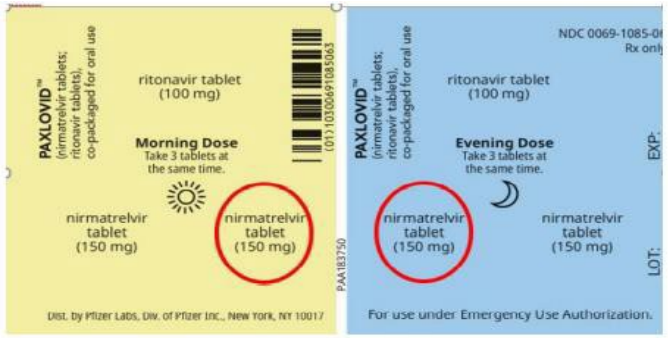


Figure 1: Remove the nirmatrelvir tablets circled in red from the blister card

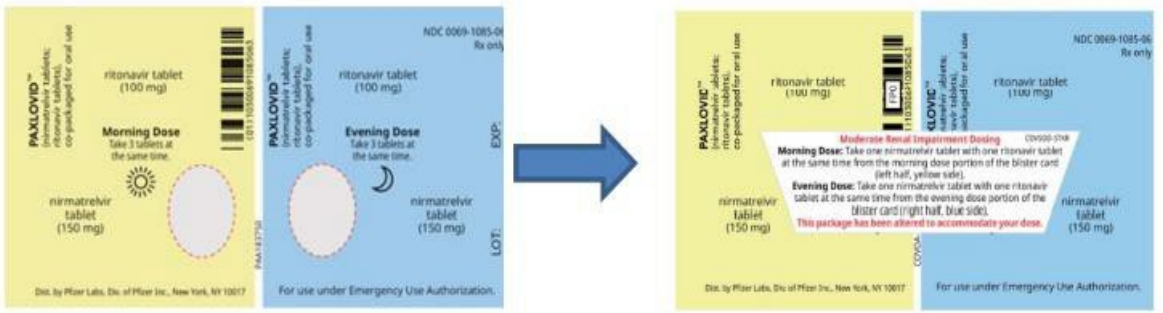


Figure 2: Placement of sticker over empty blister cavities and pre-printed dosing instruction after removal of nirmatrelvir tablets

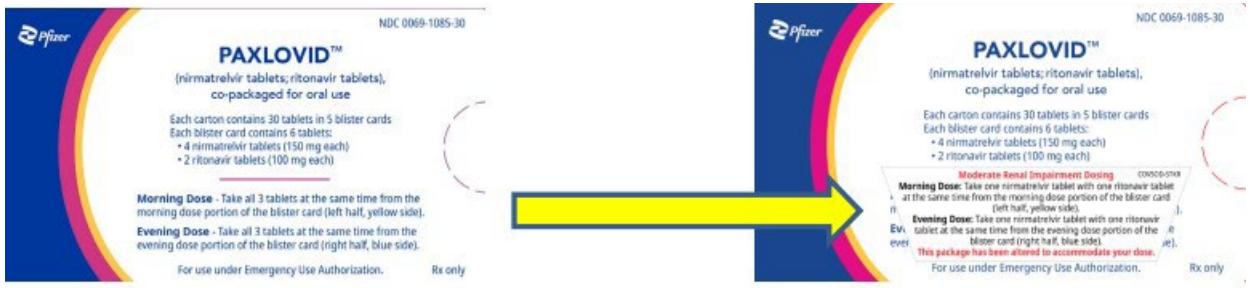


Figure 3: Placement of sticker over pre-printed dosing regimen on carton

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

Nirmatrelvir plus Ritonavir Drug-Drug Interactions

https://covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/

https://covid19-druginteractions.org/checker

Nirmatrelvir plus Ritonavir Interactions

Medications Without Clinically Relevant Interactions

These commonly prescribed medications may be co-administered without dose adjustment and without increased monitoring. This list is not inclusive of all noninteracting medications within each drug category.

Acid reducing agents
- Famotidine
- Omeprazole
- Pantoprazole

Allergy medications
- Cetirizine
- Diphenhydramine
- Loratadine

Anti-infective agents
- Azithromycin
- Hydroxychloroquine

Diabetes medications
- Empagliflozin
- Insulin
- Metformin
- Pioglitazone

Immunosuppressants
- Methotrexate
- Mycophenolate
- Prednisone

Lipid-modifying agents
- Ezetimibe

Pain medications
- Acetaminophen
- Aspirin
- Codeine
- Ibuprofen
- Naproxen

Respiratory medications
- Corticosteroids (inhaled)
- Formoterol
- Montelukast

Adjust Concomitant Medication Dose and Monitor for Adverse Effects.

Consult the Liverpool COVID-19 Drug Interactions website or the Ontario COVID-19 Science Advisory Table for specific dosing recommendations. If the dose of the concomitant medication cannot be adjusted. withhold the medication (if clinically appropriate) or use an alternative concomitant medication or COVID-19 therapy.

Temporarily Withhold Concomitant Medication, If Clinically Appropriate

With hold these medications during ritonavir-boosted nirmatrelvir treatment and for at least 2-3 days after treatment completion. They may need to be withheld for longer if the patient 1s elderly or the medication has a long half- life. If withholding is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy.

Prescribe Alternative COVID-19 Therapy.

For these medications. management strategies are not possible or feasible, or the risks outweigh the potential benefits.

Paxlovid (nirmatrelvir and ritonavir) 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 CYP3A for clearance and for which elevated concentrations are associated with severe/life-threatening reactions*	• Alpha1-adrenoreceptor antagonists: alfuzosin • Analgesics: pethidine, 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: carbamazepine, phenobarbital, phenytoin • Antimycobacterials: rifampin • Herbal product: St John's Wort (*hypericum perforatum)*

***NOT COMPLETE LIST OF ALL DDI's. ALWAYS USE Liverpool Covid-19 interaction checker AND CLINICAL JUDGMENT** (https://covid19-druginteractions.org)
For more information see: NIH COVID-19 Treatment Guidelines Panel's Statement on Ritonavir-Boosted Nirmatrelvir (Paxlovid) (https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-paxlovid-drug-drug-interactions/); Fact Sheet for Healthcare Providers for Paxlovid (nirmatrelvir and ritonavir) (https://www.fda.gov/media/155050/download); **and** Pfizer's Toolkit (https://pfizermedical.pfizerpro.com/infectious-disease)

Additional Paxlovid Prescribing Resources

1. University of Liverpool COVID-19 Drug Interactions: https://covid19-druginteractions.org/checker
2. FDA PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers: https://www.fda.gov/media/158165/download
3. Pfizer Drug Interaction Checker: https://www.pfizermedicalinformation.com/en- us/drug-interaction-checker?product=PAXLOVID%E2%84%A2+%7C+nirmatrelvir+tablets%3B+ritonavir+tablets&product2=Alfuzosin
4. NIH COVID-19 Treatment Guidelines - Ritonavir-Boosted Nirmatrelvir (Paxlovid): https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/
5. CDC/IDSA COVID-19 Clinician Call: All About Paxlovid; Plus Variants Update: https://www.idsociety.org/multimedia/clinician-calls/cdcidsa-covid-19-clinician- call-all-about-paxlovid-plus-variants-update/

Related Resources: Paxlovid

Additional Paxlovid Prescribing Resources

- University of Liverpool COVID-19 Drug Interactions
- FDA PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers
- Pfizer Drug Interaction Checker
- NIH COVID-19 Treatment Guidelines - Ritonavir-Boosted Nirmatrelvir (Paxlovid)
- CDC/IDSA COVID-19 Clinician Call Recording: All About Paxlovid; Plus Variants Update

COVID-19 Rebound

- Recent case reports document that some patients with normal immune response who have completed a 5-day course of Paxlovid for laboratory-confirmed infection and have recovered can experience recurrent illness 2 to 8 days later, including patients who have been vaccinated and/or boosted.
  - Both the recurrence of illness and positive test results improved or resolved without additional antiviral treatment.

COVID-19 Rebound

- In the Paxlovid clinical trial supporting the EUA (EPIC-HR), a small number of participants had one or more positive SARS-CoV-2 RT-PCR test results after testing negative, or an increase in the amount of SARS-CoV-2 detected by PCR, after completing their treatment course (NP swab samples). This finding was observed in persons randomized to Paxlovid and in persons randomized to placebo.
  - There was no increased occurrence of hospitalization or death, and there was no evidence that the rebound in detectable viral RNA was the result of SARS-CoV-2 resistance to Paxlovid.

COVID-19 Rebound

- There is currently no evidence that additional treatment for COVID-19 is needed for COVID-19 rebound.
- These reports do not change the conclusions from the Paxlovid clinical trial which demonstrated a marked reduction in hospitalization and death.
- Electronic Health Record based data analyses may more fully characterize incidence and risk of disease progression associated with COVID-19 rebound. However, prospective data are likely needed to fully understand pathophysiology and association with drug treatment.

CDC Health Advisory: https://emergency.cdc.gov/han/2022/han00467.asp

CDC Health Advisory
COVID-19 Rebound After Paxlovid Treatment

- The Centers for Disease Control and Prevention (CDC) is issuing this Health Alert Network (HAN) Health Advisory to update healthcare providers, public health departments, and the public on the potential for recurrence of COVID-19 or "COVID-19 rebound."

- **Paxlovid continues to be recommended for early-stage treatment of mild to moderate COVID-19 among persons at high risk for progression to severe disease**.
- Paxlovid treatment helps prevent hospitalization and death due to COVID-19. COVID-19 rebound has been reported to occur between 2 and 8 days after initial recovery and is characterized by a recurrence of COVID-19 symptoms or a new positive viral test after having tested negative.
- **A brief return of symptoms may be part of the natural history of SARS-CoV-2 (the virus that causes COVID-19) infection in some persons, independent of treatment with Paxlovid and regardless of vaccination status**.
- Limited information currently available from case reports suggests that persons treated with Paxlovid who experience COVID-19 rebound have had mild illness; there are no reports of severe disease.

COVID-19 Rebound After Paxlovid Treatment (cdc.gov)

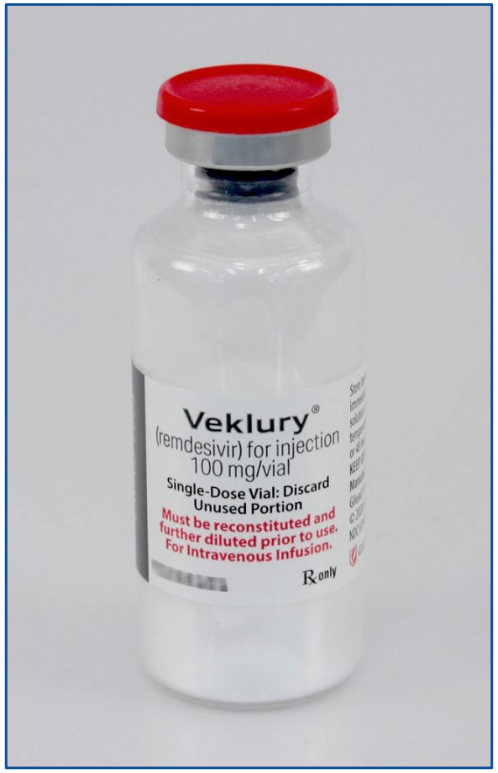
Essential elements of a Paxlovid prescription

- **Numeric dose of each active ingredient within PAXLOVID**
- **Dispense-by date (i.e., within 5 days of symptom onset)**
- ***Optional:* Renal function**
- ***Optional:* Medication list reviewed/reconciled**

- *Prescribers writing prescriptions for Paxlovid should include the dispense-by date (i.e., within 5 days of the symptom onset date) and are encouraged to include information about the patient's renal function and a statement that the patient's medication list has been reviewed/reconciled. For further information, refer to FDA's PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers (https://www.fda.gov/media/158165/download).*

Veklury (remdesivir)

Veklury (remdesivir) – Gilead
Antiviral for IV Infusion



Veklury Product Information

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) Prescribing Information

Veklury

Veklury (remdesivir) is a nucleotide analog RNA polymerase inhibitor

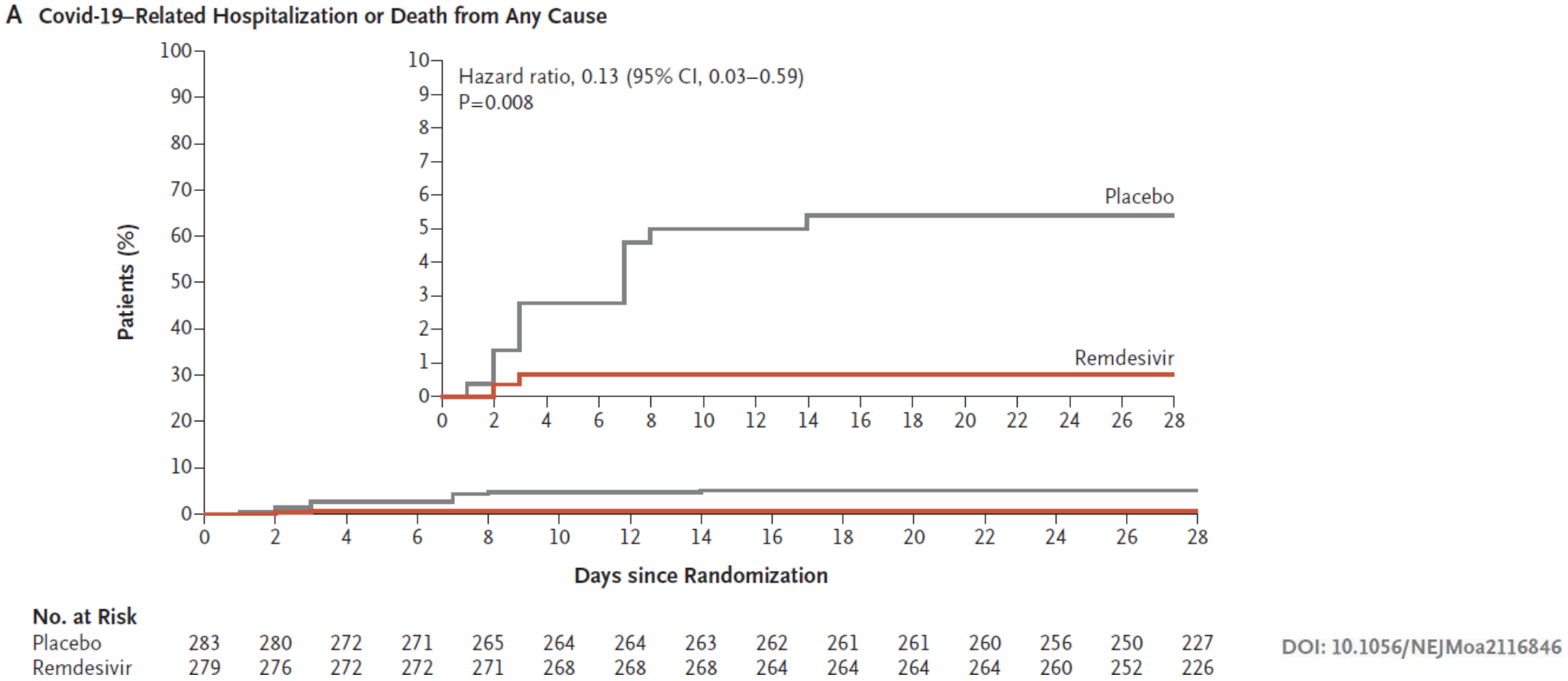
- Regulatory Status: Approved Drug
- Age Range: adults and pediatric patients (28 days and older and weighing at least 3 kg)
- Dosing (non-hospitalized): a single loading dose on Day 1 (200 mg or 5 mg/kg) followed by once-daily maintenance doses on Days 2 and 3 (100 mg or 2.5 mg/kg) by intravenous infusion

Veklury

- Timing: as soon as possible after COVID-19 diagnosis and within 7 days of symptom onset
- Special Consideration – Renal Impairment: Not recommended in patients with eGFR less than 30 mL/min
- Special Consideration – Hypersensitivity Reactions: Monitor patients during infusion and for at least one hour after infusion is complete.
- Special Consideration - Chloroquine: Potential antagonistic effect of chloroquine on antiviral activity of Veklury

Early Remdesivir to Prevent Progression to Severe COVID-19 in Outpatients

R.L. Gottlieb, C.E. Vaca, R. Paredes,J. Mera, B.J. Webb, G. Perez, G. Oguchi, P. Ryan, B.U. Nielsen, M. Brown, A. Hidalgo, Y. Sachdeva, S. Mittal, 0. Osiyemi, J. Skarbinski, K.Juneja, R.H. Hyland, A. Osinusi, S. Chen, G. Camus, M. Abdelghany, S. Davies, N. Behenna-Renton, F. Duff, F.M. Marty,* M.J. Katz, A.A. Ginde, S.M. Brown, J.T. Schiffer, and J.A. Hill, for the GS-US-540-9012 (PINETREE) Investigators†



DOI: 10.1056/NEJMoa2116846

Related Resources: Veklury (remdesivir)

Additional Veklury (remdesivir) Prescribing Resources

- Prescribing Information & FDA Fact Sheets
  - Veklury (remdesivir) Prescribing Information
  - Veklury Patient Information
- Manufacturer's Resources:
  - Website for Healthcare Providers
  - Website for Patients
- Additional Resources:
  - NIH's COVID-19 Treatment Guidelines Therapeutic Management of Nonhospitalized Adults With COVID-19
  - FDA MedWatch
  - Safety Reporting Email

Remdesivir: Gilead patient assistance program

- Gilead program that covers assistance for commercially-insured patients
  - Patients who are not insured can get relieve via the Cares Act and Provider Relief Fund

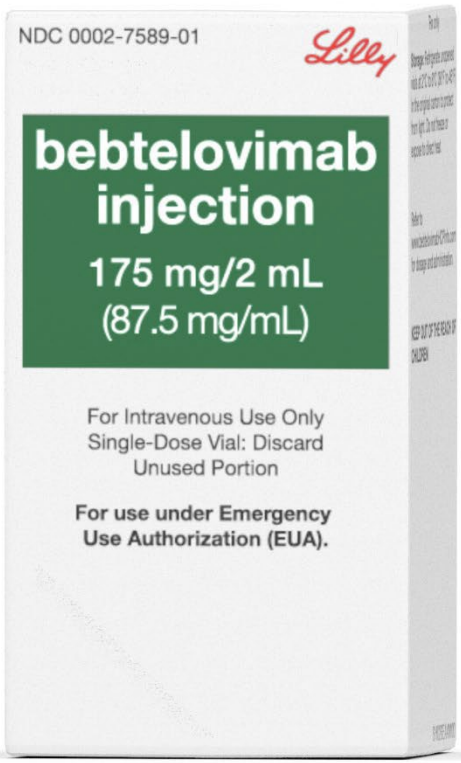
- The amount of financial assistance depends on the patient's health insurance plan, deductible, and level of need
  - There is a copay coupon for those with commercial insurance, depending on the type of insurance

- Resources for HCPs: https://www.gileadadvancingaccess.com/hcp/resources
  - sample letter of medical necessity, sample letter of appeal and prior authorization checklist)

- Enrollment form: https://services.gileadhiv.com/content/pdf/gilead_enrollment_form.pdf
  - Can be completed online and then saved (you can download the application)

bebtelovimab (monoclonal antibody)

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



bebtelovimab Product Information

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 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

Bebtelovimab is a human IgG1 monoclonal antibody targeting the SARS-CoV-2 spike protein.

- Regulatory Status: Emergency Use Authorization limited to patients for whom alternative COVID-19 treatment options are not accessible or clinically appropriate
- Age Range: adults and pediatric patients (12 years of age and older and weighing at least 40 kg)
- Dosing: 175 mg administered as a single intravenous injection over at least 30 seconds

Bebtelovimab

- Timing: as soon as possible after COVID-19 diagnosis and within 7 days of symptom onset
- Special Consideration – Hypersensitivity Reactions: Monitor patients during infusion and for at least one hour after infusion is complete.
- Special Consideration – Variants: Based on authentic virus and/or pseudotyped virus like-particle neutralization data, no reduction in susceptibility to BA.1.1, BA.2, and BA.2.12.1.

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR BEBTELOVIMAB

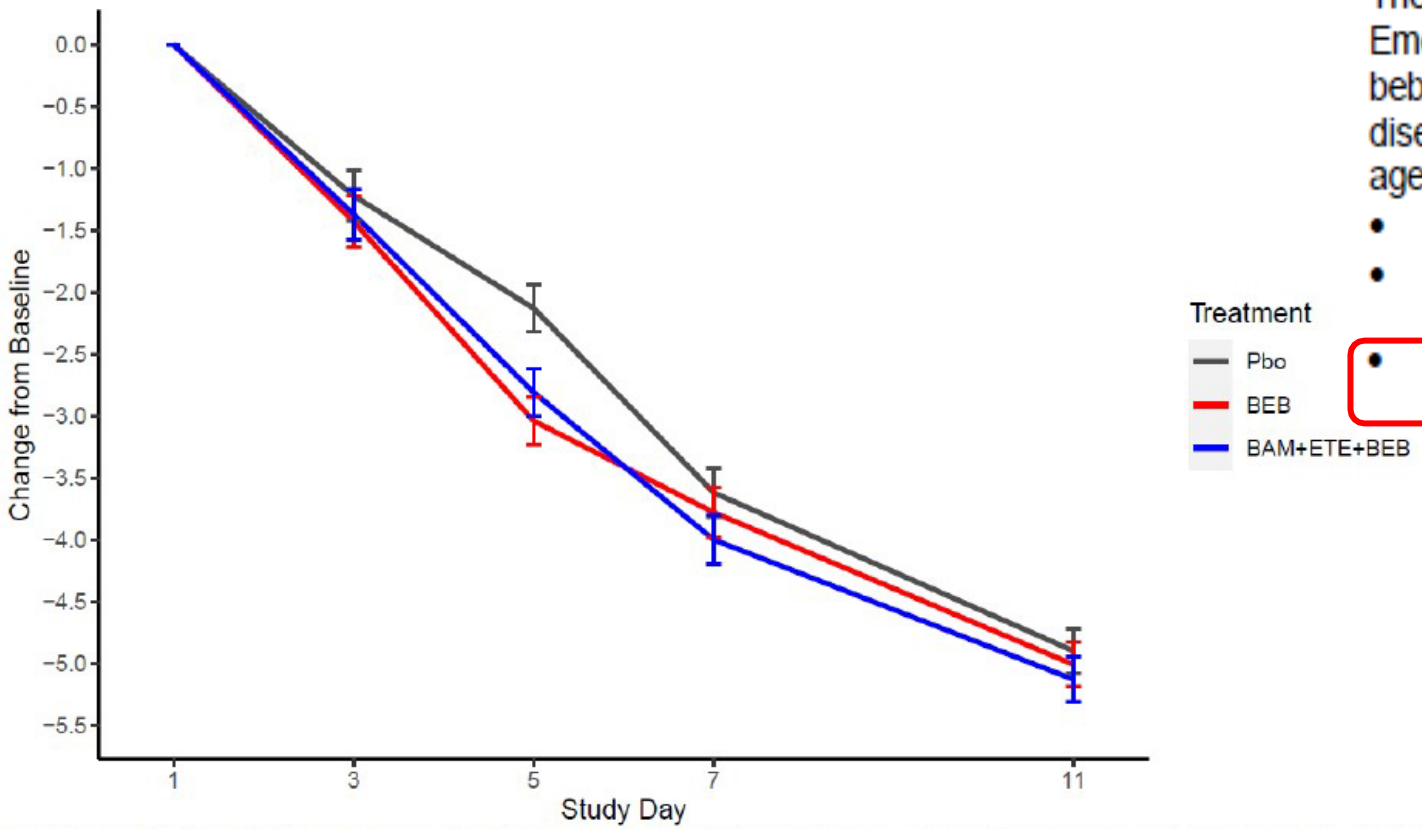


Figure 1: SARS-CoV-2 Viral Load Change from Baseline (Mean ± SE) by Visit from the Placebo-Controlled Portion of BLAZE-4 in Low Risk Adults (700 mg bamlanivimab, 1,400 mg etesevimab, 175 mg bebtelovimab together and 175 mg bebtelovimab alone).

----------EMERGENCY USE AUTHORIZATION----------

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of bebtelovimab for the treatment of mild-to-moderate coronavirus disease 2019 (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 approved or authorized by FDA are not accessible or clinically appropriate.

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

Related Resources: Bebtelovimab

Additional Bebtelovimab Prescribing Resources

- FDA Fact Sheets
  - Bebtelovimab provider fact sheet
  - Bebtelovimab patient fact sheet
  - Bebtelovimab patient fact sheet (Spanish)
- Manufacturer's Resources:
  - Website for Healthcare Providers
  - Website for Patients
- Additional Resources:
  - NIH's COVID-19 Treatment Guidelines Therapeutic Management of Nonhospitalized Adults With COVID-19
  - COVID-19 Therapeutics Locator
  - FDA MedWatch
  - Safety Reporting Email
  - ASPR Clinical Implementation Guide: Module 4 Monoclonal Antibody Administration

Strategies for conserving bebtelovimab supply

Best practices	• Paxlovid is first-line therapy for patients presenting within 5 days of onset of COVID-19 symptoms: address drug interactions that can be altered safely • Bebtelovimab referral form that requires reason for not prescribing Paxlovid
Common situations where bebtelovimab is appropriate for use	• Patients presenting between 6–7 days after symptom onset • Drug-drug interactions that cannot be addressed safely • Renal clearance too low to dose-adjust Paxlovid (i.e., GFR <30) • Swallowing issues (including severe throat pain from COVID-19) • Concerns over loss to follow-up or inability to complete Paxlovid course
Situations where bebtelovimab should be avoided if possible	• Default treatment option for pregnancy • Provider is unable to assess renal function for Paxlovid • Drug-drug interaction that is “too complicated” for provider to navigate • Patient preference (heard mAb is better, or prior experience) • Provider preference (without medical/behavioral rationale) • Patients unwilling to risk side-effects from Paxlovid (rebound/isolation)

Lagevrio (molnupiravir)

Lagevrio (molnupiravir) – Merck
Oral Antiviral

Lagevrio™
molnupiravir 200 mg capsules

[Lagevrio (molnupiravir) Product Information]

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)

Lagevrio

Lagevrio (molnupiravir) is a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis.

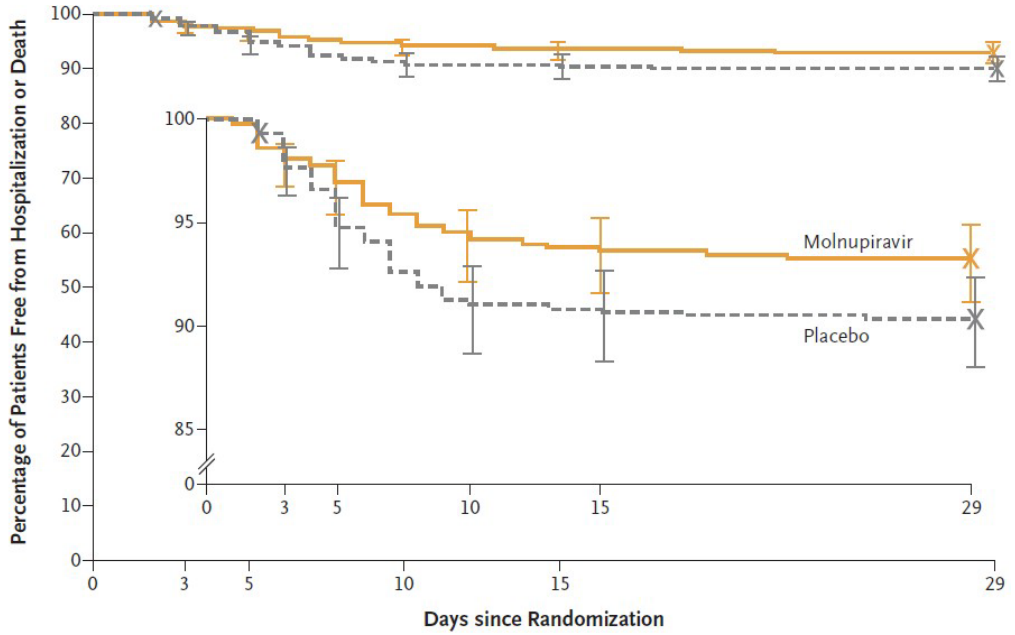
- Regulatory Status: Emergency Use Authorization limited to patients for whom alternative COVID-19 treatment options are not accessible or clinically appropriate
- Age Range: Not authorized for use in patients less than 18 years of age
- Dosing: 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food

Lagevrio

- Timing: as soon as possible after COVID-19 diagnosis and within 5 days of symptom onset
- Special Consideration – Embryo-Fetal Toxicity: Not recommended for use during pregnancy
- Special Consideration – Bone and Cartilage Toxicity: Not authorized for use in patients less than 18 years age because it may affect bone and cartilage growth
- Special Consideration – Contraception: Females for duration of treatment and 4 days after the last dose. Males during treatment and 3 months after the last dose (Risk beyond 3 months unknown; nonclinical studies not yet completed)

Molnupiravir for Oral Treatment of COVID-19 in Nonhospitalized Patients

A. Jayk Bernal, M.M. Gomes da Silva, D.B. Musungaie, E. Kovalchuk, A. Gonzalez, V. Delos Reyes, A. Martin-Quiros, Y. Caraco, A. Williams-Diaz, M.L. Brown, J. Du, A. Pedley, C. Assaid, J. Strizki, J.A. Grobler, H.H. Shamsuddin, R. Tipping, H. Wan, A. Paschke, J.R. Butterton, M.G.Johnson, and C. De Anda, for the MOVe-OUT Study Group*



No. at Risk						
Molnupiravir	709	699	693	670	665	661
Placebo	699	693	674	637	634	631
No. of Events						
Molnupiravir	10	6	23	5	4	0
Placebo	5	19	37	3	3	0

N Engl J Med 2022;386:509-20.
DOI: 10.1056/NEJMoa2116044

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.

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
     https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program

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

Lagevrio (molnupiravir) Prescriber Requirements (continued)

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.**

Related Resources: Lagevrio (molnupiravir)

Additional Lagevrio Prescribing Resources

- FDA Lagevrio Fact Sheet for Providers
- FDA Lagevrio Fact Sheet for Patients
- Pfizer Drug Interaction Checker
- NIH COVID-19 Treatment Guidelines – Lagevrio (molnupiravir)

Accessing COVID-19 Therapeutics: Community Access & Resources

Kristen McAuley, MPH
Director, Public Health Planning
Maine Center for Disease Control & Prevention
Maine Department of Health & Human Services

Federal & State Resources

- ASPR Test to Treat Locator: covid-19-test-to-treat-locator.dhhs.hub.arcgis.com
  - Specific to Oral Antivirals
  - Search “ASPR Test to Treat”
- ASPR COVID-19 Therapeutics Locator: covid-19-therapeutics-locator-dhhs.hub.arcgis.com
  - Includes Oral Antivirals, mAb, Evusheld
  - Search “ASPR Therapeutics Locator”
- COVID-19 Treatment in Maine: maine.gov/COVID19/treatment
  - Search “Maine COVID Treatment”

COVID-19 Therapeutics: Community Placement & Access

- If a patient is COVID-19+ and needs a prescription for Paxlovid or Lagevrio…

- Oral Antiviral Placement
  - Retail chain pharmacies, including most Hannafords, Walmart, Walgreens, Shaw's, and CVS.
  - Some independent pharmacies maintain inventory, such as Community Pharmacy, Nathan's Pharmacy, and others.
  - Some retail pharmacies based in hospitals, such as Maine Medical Center and Northern Light Health pharmacies

Community Placement & Access: ASPR Test to Treat Locator

Find COVID-19 Medication

Portland, ME, USA

10 mi

0 — 250

Results:54

- Locations with testing, medical visits, and medication (Test-to-Treat) 3
- Locations to fill a prescription 51

How to get medication

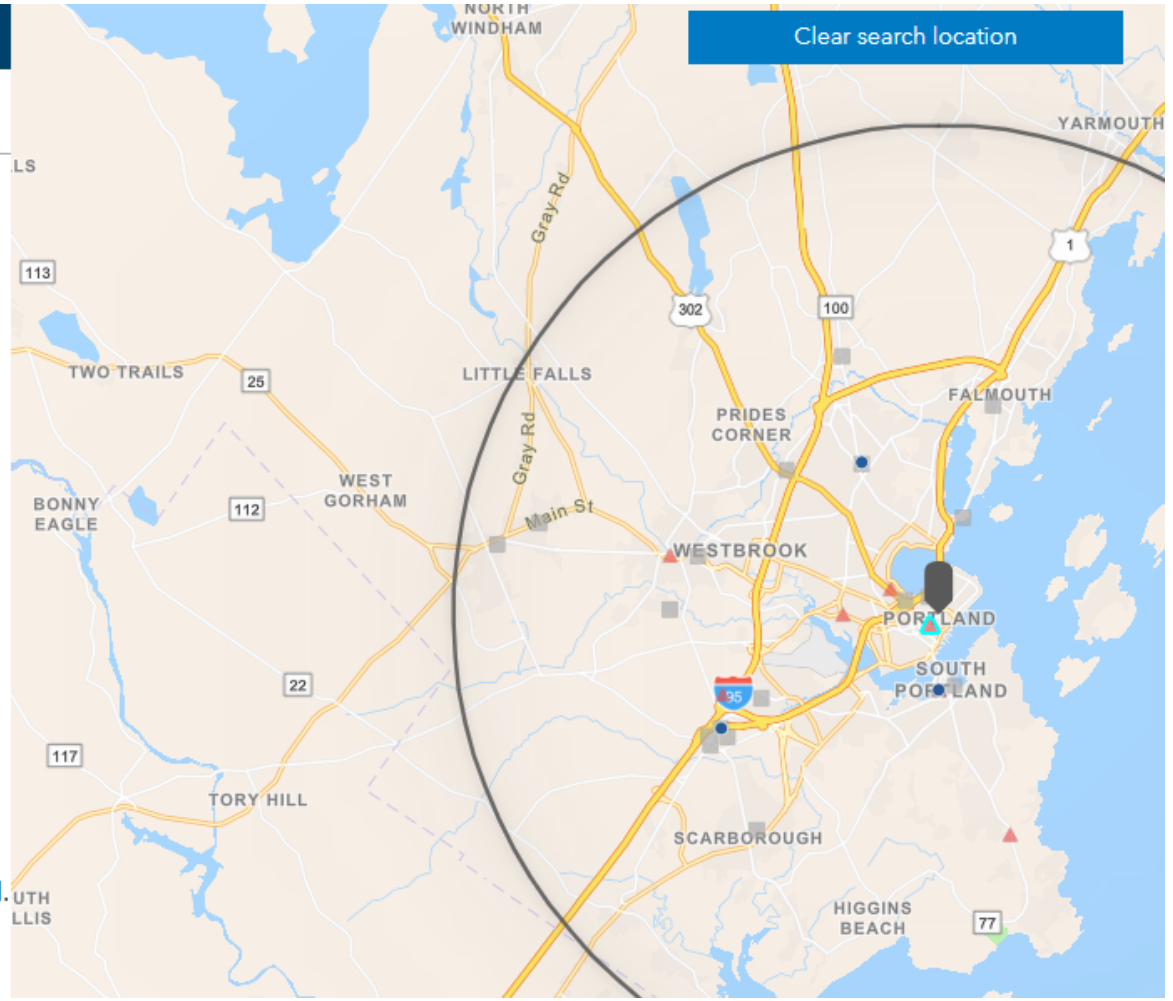
1. Locations to get testing, medical visits, and medication (Test-to-Treat)

Some pharmacy clinics and health centers can prescribe and give you medication at the same location.

Learn more about the Test-to-Treat program.

2. Locations to fill a prescription

Any healthcare provider can evaluate and prescribe you COVID-19 medication just as they normally would. You can fill those prescriptions at any location in this tool.



Community Placement & Access: ASPR Test to Treat Locator

Find COVID-19 Medication

Portland, ME, USA

10 mi

0 250

Results:54

Locations with testing, medical visits, and medication (Test-to-Treat) 3

Locations to fill a prescription 51

CVS Store #00454 (0.29 mi)

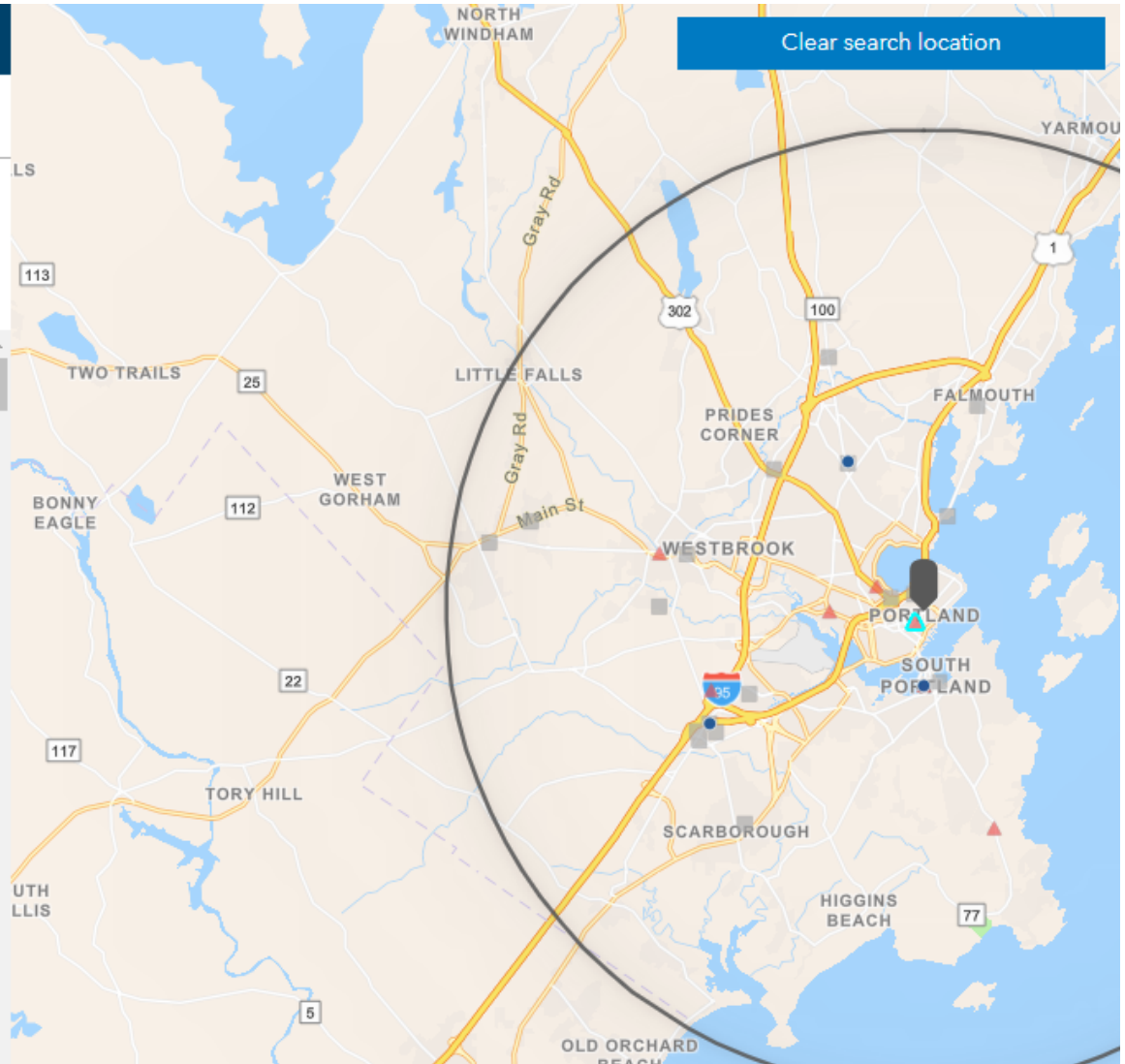
510 Congress Street, Portland, ME 04101
Therapeutic: Paxlovid

If you have tested positive for COVID-19 talk to your doctor, visit a local community health center, or this location offers the option to schedule a telehealth appointment with a provider who can assess your eligibility and prescribe an oral antiviral to a pharmacy of your choice.

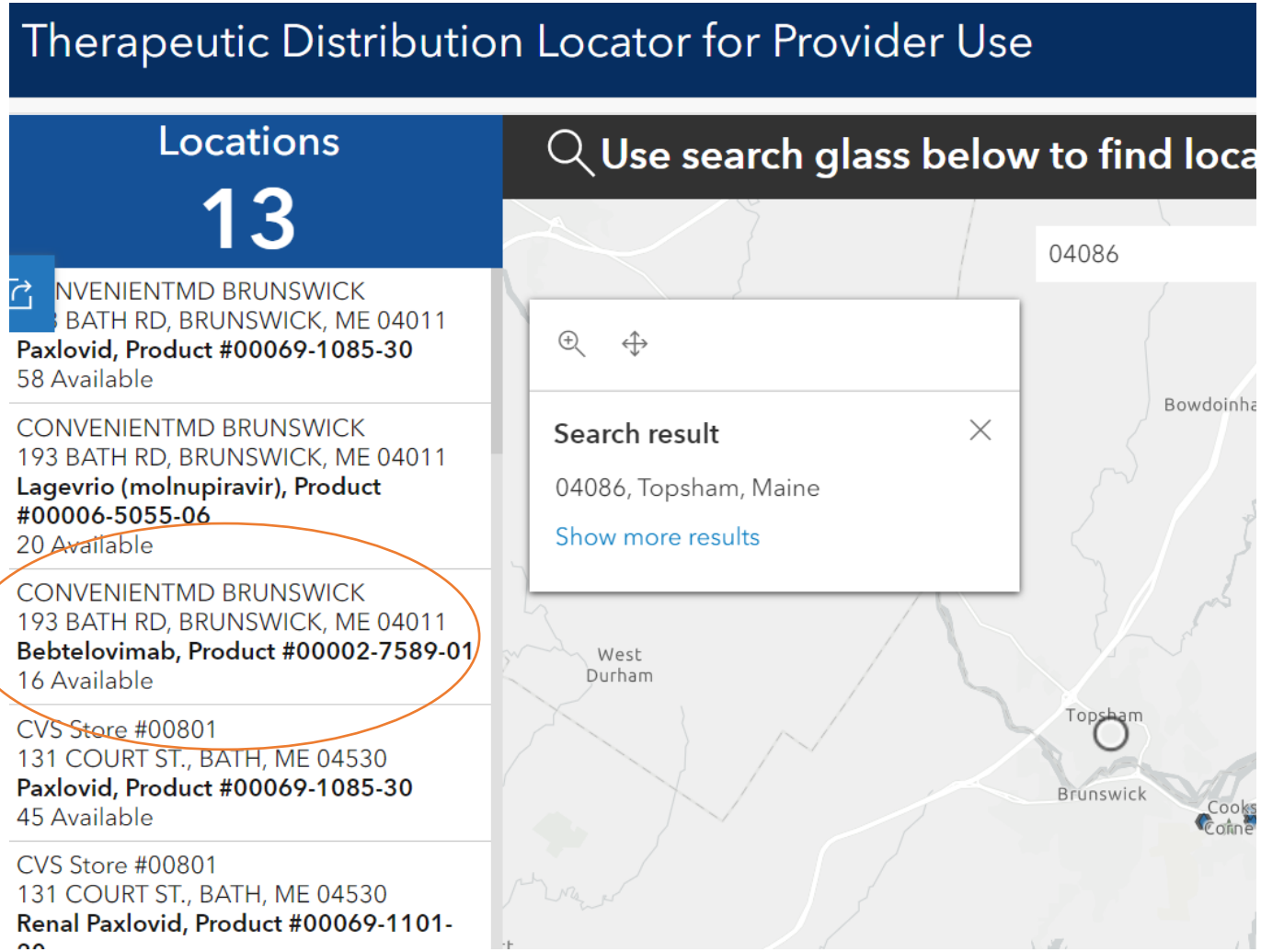
CVS Store #00454 (0.29 mi)

510 Congress Street, Portland, ME 04101
Therapeutic: Lagevrio (molnupiravir)

If you have tested positive for COVID-19 talk to your doctor, visit a local community health center, or this location offers the option to schedule a telehealth appointment with a provider who can assess your eligibility and prescribe an oral antiviral to a pharmacy of your choice.



Community Placement & Access: ASPR Therapeutics Locator



COVID-19 Therapeutics:
Maine COVID-19 Treatment Website

Where to Get Treated

Where can I fill a prescription in Maine?

If you have already received a prescription for medication you can find a pharmacy at this link for locations to fill a prescription.

Where can I get tested, be seen by a provider, and get treated (Test-to-Treat site) in Maine?

Your doctor can prescribe medication for COVID-19. Additionally, anyone in Maine can go to any of the following locations to get tested, be seen by a medical provider, and get treated.

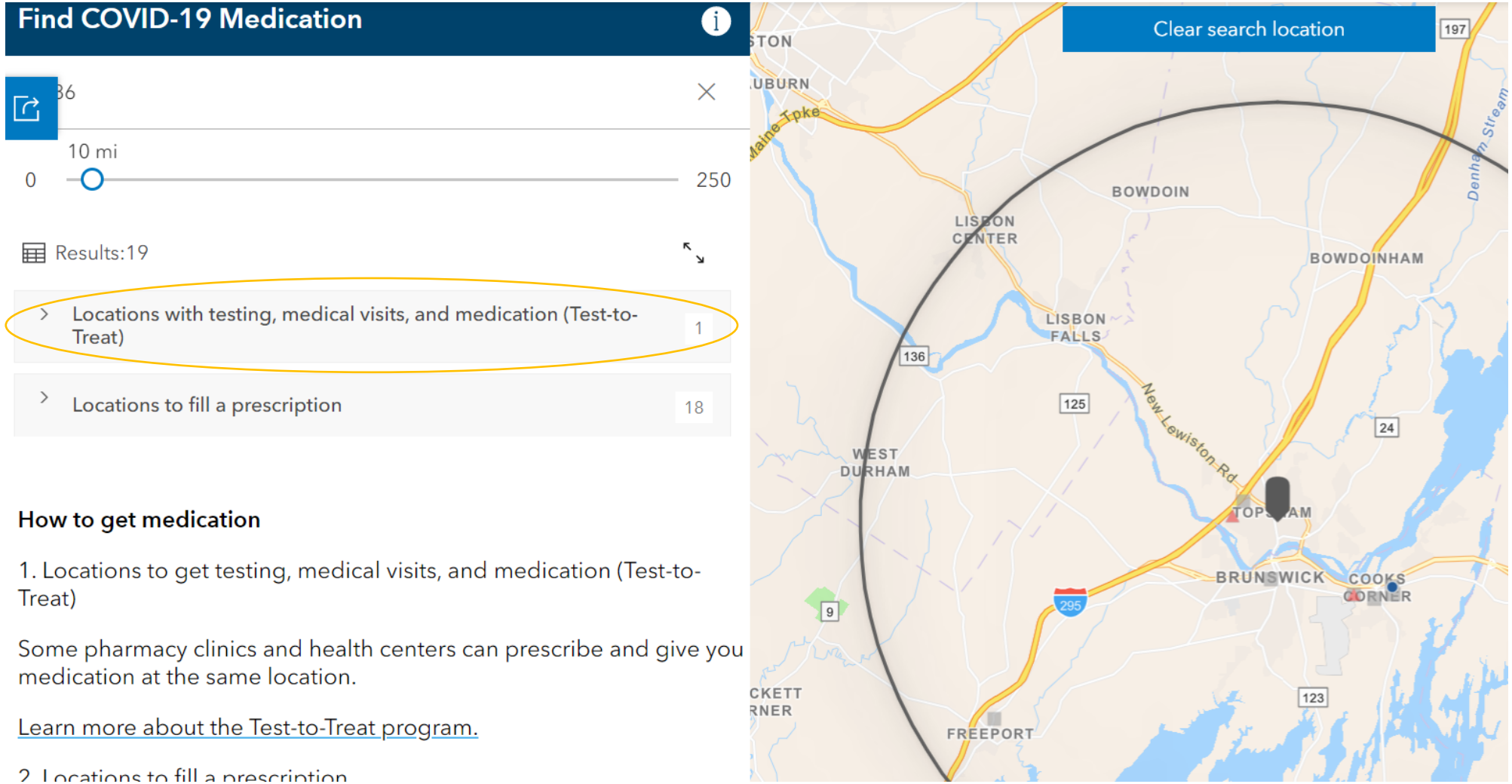
All sites are open to the public.

Find a provider nearest you and contact that location for more information before going to any of these locations.

Most medications are provided free of charge; but you may be asked for insurance information.

Provider	Address	Contact Info
Bridgton Hospital	10 Hospital Drive, Bridgton	207-330-7352
Cary Medical Center	163 Van Buren Rd, Caribou ME 04736	207-498-3111
Central Maine Medical Center	300 Main Street, Lewiston, ME 04240	207-330-7352
ConvenientMD Urgent Care Bangor	543 Broadway, Bangor, ME 04401	207-922-1300 More info
ConvenientMD Urgent Care Brunswick	193 Bath Road, Brunswick, ME 4011	207-424-2272 More info
ConvenientMD Urgent Care Portland	191 Marginal Way, Portland ME 04101	207-517-3838 More info
ConvenientMD Urgent Care Ellsworth	235 High Street, Ellsworth	207-412-5200 More info
ConvenientMD Urgent Care Saco	506 Main Street, Saco	207-751-7991 More info
ConvenientMD Urgent Care Westbrook	950 Main Street, Westbrook	207-517-3800 More info
MaineGeneral Express Care Augusta	15 Enterprise Drive, Augusta	207-621-8880
MaineGeneral Express Care Waterville	211 Main Street, Waterville	207-877-3450
MaineGeneral Express Care Winthrop	16 Commerce Plaza, Suite 3A, Winthrop	207-377-1450

COVID-19 Therapeutics: Patient Assessment Considerations



COVID-19 Therapeutics: Patient Assessment Considerations

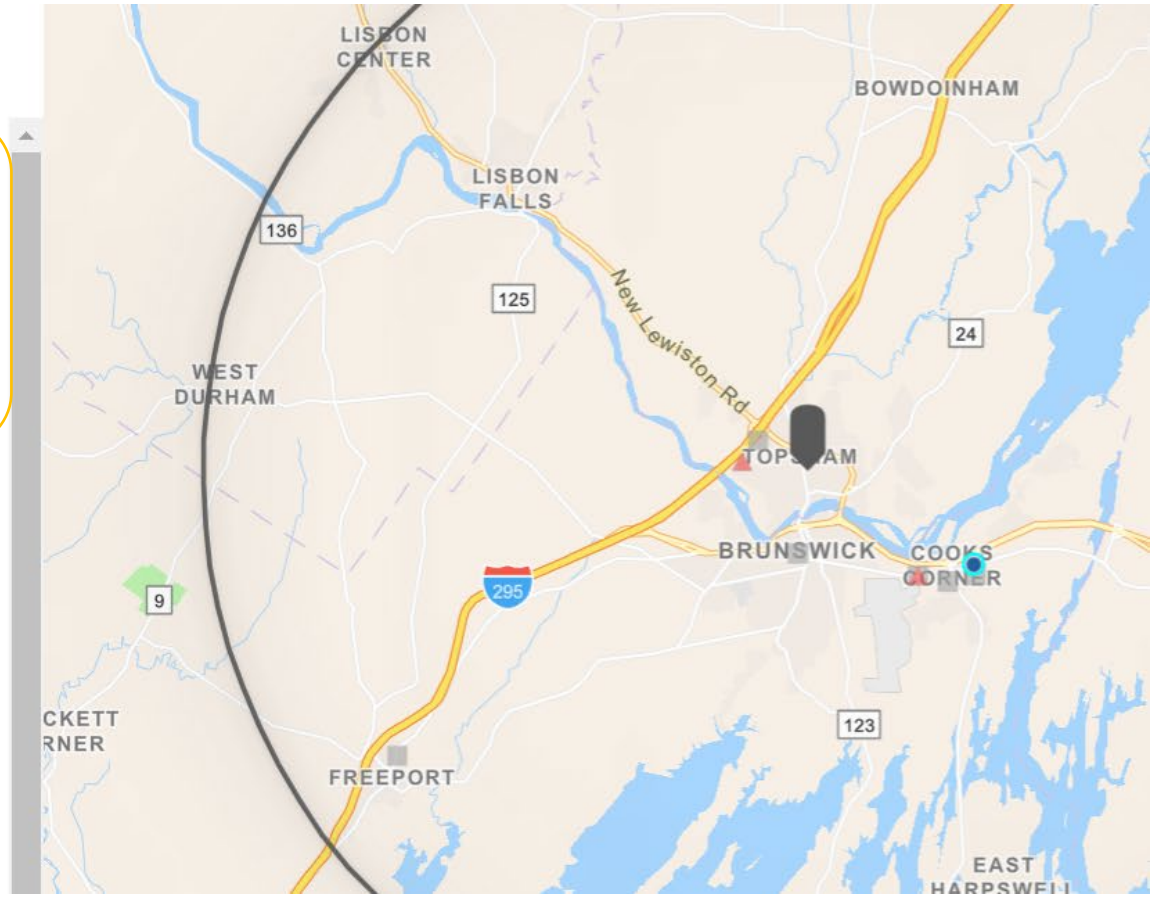
Results:19

Locations with testing, medical visits, and medication (Test-to-Treat) 1

Convenientmd Brunswick (3.11 mi)

193 Bath Rd, Brunswick, ME 04011
To book an appointment, call: 207-424-2272

Locations to fill a prescription 18



How to get medication

1. Locations to get testing, medical visits, and medication (Test-to-Treat)

Some pharmacy clinics and health centers can prescribe and give

Mild COVID

Aaron Karmes, DO
Medical Director
COVID Treatment Center
St. Joseph Hospital (Bangor), Covenant Health

STATE OF MAINE
Department of
Health and Human Services

COVENANT HEALTH

MaineHealth

Maine Osteopathic Association

Northern Light Health

Maine Medical Association

Mild COVID

Patient presentation	• 65-year-old male, call to PCP office, has COVID symptoms, positive home test.
Findings/attributes	• Day 3. Sore throat and nasal congestion. Home test kit today, positive • Primary mRNA vaccine series, first booster, second booster 3 weeks ago • BMI 26, HTN on lisinopril, HLD on statin, NKDA
Clinical decision	• Offer treatment with Paxlovid
Key points/notes	• Goal is early treatment to prevent progression to severe COVID • Offer treatment based on risk for severe disease, not based on symptoms • 4 doses of COVID-19 vaccine are strongly protective against severe disease • Avoid ‘wait and see’ approach • COVID-19 rebound is rare • Paxlovid is first line therapy

Positive test and no COVID Symptoms

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Medical Director
COVID Treatment Center
St. Joseph Hospital (Bangor), Covenant Health

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Positive test and no COVID Symptoms

Patient presentation	• 73-year-old female calls PCP office, positive rapid antigen test
Findings/attributes	• Asymptomatic • Primary mRNA vaccine series complete, received two boosters • COPD with no daily symptoms and infrequent exacerbations
Clinical decision	• No treatment indicated
Key points/notes	• No treatment is indicated for asymptomatic infection • Have a plan to obtain treatment • Oral COVID therapeutics are readily available

47 yo M: Mild COVID

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Waldo County General Hospital
Covid-19 Response Site Director
Maine Health

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Department of
Health and Human Services

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Maine Osteopathic Association

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Maine Medical Association

47 yo M with obesity & smoking history: Mild COVID

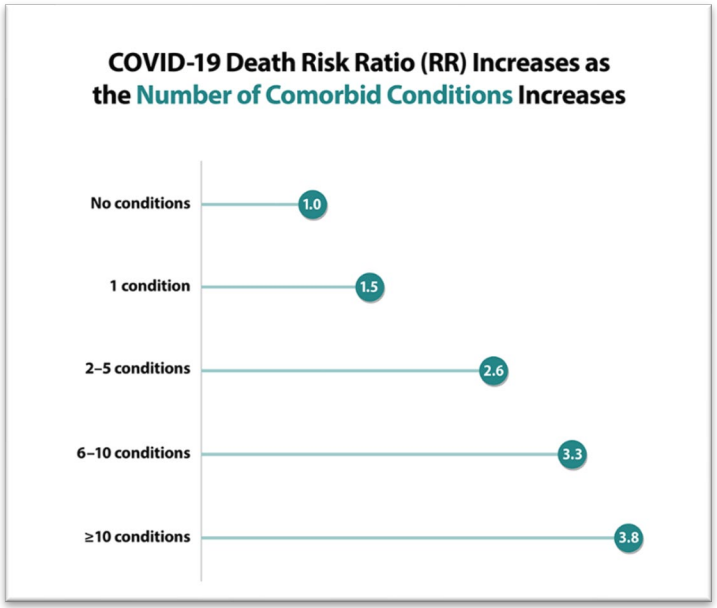
Patient presentation	• 47 yo M calls PCP to report positive home Covid-19 test
Findings/attributes	• Day 3 of symptoms. Started with sore throat and nasal congestion. Now sore throat, nasal congestion, non-productive cough, no fever, no dyspnea, no myalgias, no GI symptoms, more fatigued than normal. • Fully vaccinated and boosted • PMH significant for obesity, BMI 38, and 20-pack-year smoking history • No daily medications, no known medication allergies
Clinical decision	• Offer treatment with Paxlovid.
Key points/notes	• He is symptomatic and within the time window for all therapeutics. He has risk factors for severe disease (obesity, smoking history) • The goal of outpatient COVID therapeutics is to treat early in the infection to prevent progression from mild-moderate to severe Covid. • The benefits of Paxlovid outweigh the risks. The “risks” are minimal; patients may experience uncomfortable/inconvenient side effects that are not dangerous, most commonly include altered sense of taste, diarrhea, increased BP, and muscle aches. Patient’s may have heard of the risk of “rebound Covid” after Paxlovid, which continues to be rare but patient’s should be counseled to follow up if symptoms recur after finishing treatment.

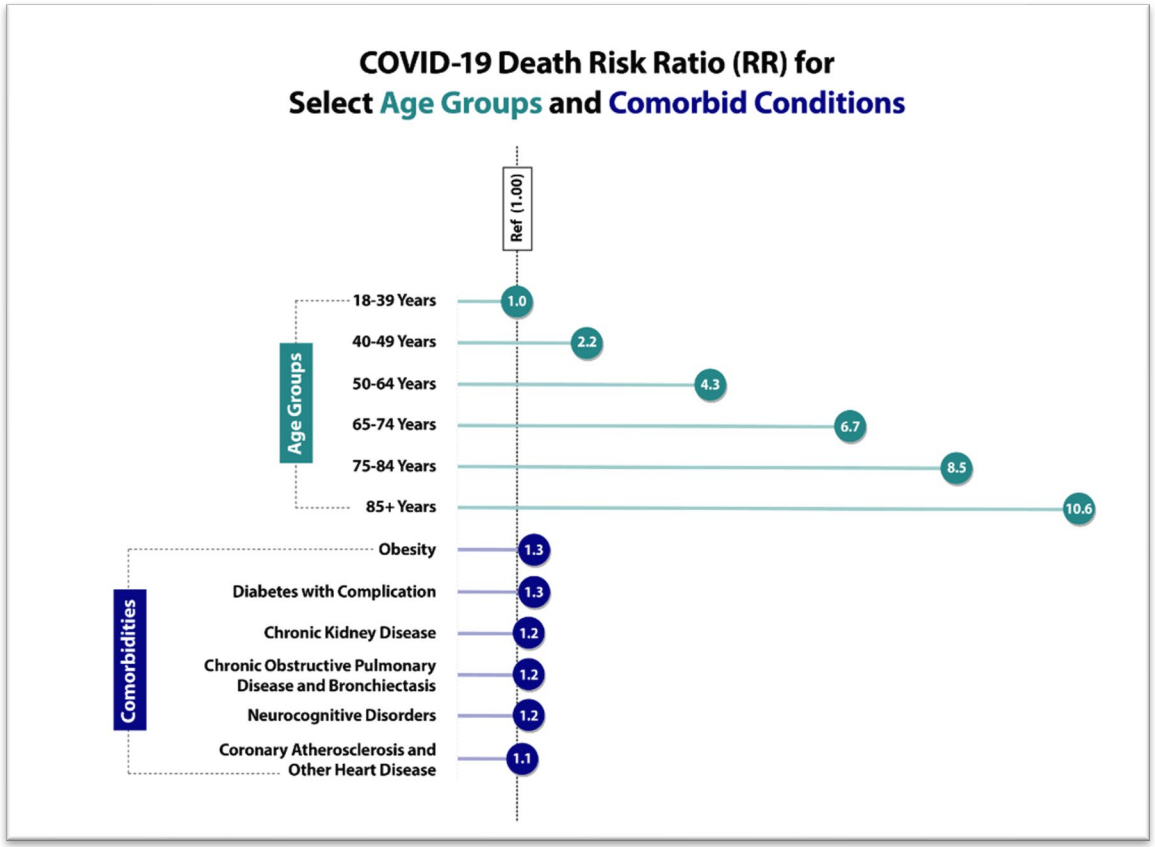
Risk for COVID-19 Infection, Hospitalization, and Death By Age Group

Updated June 2, 2022 Print

Age group rate ratios compared to ages 18 to 29 years[1]

Rate compared to 18-29 years old[1]	0-4 years old	5-17 years old	18-29 years old	30-39 years old	40-49 years old	50-64 years old	65-74 years old	75-84 years old	85+ years old
Cases[2]	<1x	1x	Reference group	1x	1x	1x	1x	1x	1x
Hospitalization[3]	1x	<1x	Reference group	2x	2x	3x	5x	8x	10x
Death[4]	<1x	<1x	Reference group	4x	10x	25x	65x	140x	330x





Risk for COVID-19 Infection, Hospitalization, and Death By Age Group | CDC

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

I. N. Patient: Positive COVID Screen

James Jarvis, MD, FAAFP
Senior Physician Executive, COVID Incident Command
Northern Light Health

STATE OF MAINE
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Northern Light Health

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I. N. Patient: Positive COVID Screen (Asymptomatic--Observe)

Patient presentation	• 76-year-old female patient admitted following a fall resulting in right ankle fracture requiring surgery. Admission screening COVID test was positive. Patient is vaccinated and has no symptoms.
Findings/attributes	• Injury and admission unrelated to COVID. • Up to date on COVID-19 vaccination and received her second booster about 8 weeks ago. She has COPD under control at present with Advair, hypertension controlled on lisinopril. SULFA allergy.
Clinical decision	• Patient should be placed under isolation precautions following local Infection Prevention Policy. • No treatment is recommended for incidental finding of positive SARS-CoV-2 infection without symptoms. • Patient should be monitored for developing symptoms. • May proceed to surgery.
Key points/notes	• Treatment should be reserved for those who are symptomatic and have at least one risk factor. • Patient should be monitored for developing symptoms and if so should be offered treatment as if she was symptomatic on admission (see Positive COVID Screen (Mild Symptoms--Treat).)

I. N. Patient: Positive COVID Screen (Mild Symptoms--Treat)

Patient presentation	• 76-year-old female patient admitted following a fall resulting in right ankle fracture requiring surgery. Admission screening COVID test was positive. Patient is vaccinated and has mild symptoms.
Findings/attributes	• Injury and admission unrelated to COVID. • Up to date on COVID-19 vaccination and received her second booster about 8 weeks ago. She has COPD under control at present with Advair, hypertension controlled on lisinopril. SULFA allergy. • She has mild cold like symptoms and a sore throat.
Clinical decision	• Patient should be placed under Isolation precautions following local Infection Prevention Policy. • Treatment is recommended for SARS-CoV-2 infection with mild symptoms and at least one risk factor for severe disease. • Paxlovid, if available, should be started following current NIH treatment guidelines. Alternatives if not available: monoclonal antibodies or remdesivir. • If admission expected to be less than 5 days (for completion of oral regimen) and compliance is in question, consider remdesivir or monoclonal antibody therapy. • May proceed to surgery if no other clinical contraindications.
Key points/notes	• Treatment is recommended for incidental finding of positive SARS-CoV-2 infection with symptoms in the same manner as you would for any outpatient with at least one risk factor for severe disease. • Patient should be monitored for developing worsening symptoms. • The goal is the same as that for outpatient COVID therapeutics, treat early in the infection before her symptoms worsen. We want to prevent progression from mild to moderate to severe COVID. Paxlovid is likely the best option for her. The data from the Paxlovid EPIC-HR trial showed the best outcomes starting within 3 days of symptom onset. We should offer her treatment based on her risk for severe disease, not based on her symptoms. She's received 4 doses of COVID-19 vaccine, which is strongly protective against severe disease, however we continue to see severe disease among some older, vaccinated adults.

Ida Grav: Pregnancy and COVID

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Senior Physician Executive, COVID Incident Command
Northern Light Health

STATE OF MAINE
Department of
Health and Human Services

COVENANT HEALTH

MaineHealth

Maine Osteopathic Association

Northern Light Health

Maine Medical Association

Ida Grav: Pregnancy and Symptomatic COVID (Treat with Paxlovid)

Patient presentation	• 24-year-old female patient G3P1 at 25 weeks EGA presents to clinic with symptoms of fever, headache, runny nose, and positive at-home COIVD rapid antigen test
Findings/attributes	• Temp 38.2 C, BP-112/62, HR-88, RR-15, FHR-135. • Pregnancy has been complicated by Medication Assisted Treatment with Subutex, doing well • Otherwise, healthy on prenatal vitamins and no known allergies. • Has not received any vaccinations against SARS-CoV-2.
Clinical decision	• Pregnancy is risk factor for severe disease and she should be offered treatment against severe disease. • Being unvaccinated is also a risk factor for severe disease. • Paxlovid should be started following current NIH treatment guidelines. • Alternatives would be monoclonal antibodies or remdesivir. • Molnupiravir (Lagevrio) is NOT recommended in pregnancy. • Once she is through her infectious period, she should be offered vaccination.
Key points/notes	• Symptoms consistent with SARS-CoV-2 infection and a positive home antigen should be considered as active infection. • Individuals who are pregnant are at high risk for severe disease and hospitalization and should be offered vaccination against SAR-CoV-2. • Paxlovid is the treatment of choice. • Remdesivir may be an option for an individual who is admitted for a non-COVID related reason who is symptomatic and tests positive for SARS-CoV-2. • There is a registry for individuals who are pregnant or become pregnant while taking Molnupiravir.

Pediatric COVID-19 Treatment

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Covid-19 Response Site Director
Maine Health

STATE OF MAINE
Department of
Health and Human Services

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General Principals

- Current evidence suggests that children with certain underlying medical conditions and infants (age <1 year) might be at increased risk for severe illness from SARS-CoV-2 infection.
- Current evidence suggests that children with medical complexity, with genetic, neurologic, metabolic conditions, or with congenital heart disease might be at increased risk for severe illness from COVID-19.
- Similar to adults, children with obesity, diabetes, asthma or chronic lung disease, sickle cell disease, or immunosuppression might also be at increased risk for severe illness from COVID-19.

Therapeutic Options

- Paxlovid
  - 12 years of age and older weighing at least 40 kg
  - Preferred treatment option
  - Within 5 days symptom onset
- Remdesivir
  - Age over 28 days and weight at least 3 kg
  - Second preferred treatment option
  - Within 7 days symptom onset
- Alternate Therapy
  - Monoclonal antibodies (currently bebtelovimab)
    - 12 years of age and older and only for use when ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir are not available, feasible to use, or clinically appropriate

14 yo F with obesity and asthma: Mild COVID

Patient presentation	• Mother of 14-year-old F patient calls PCP office to report positive home Covid-19 test
Findings/attributes	• Day 2 of symptoms. Started with sore throat and nasal congestion. Now sore throat, nasal congestion, non-productive cough, nausea, fever up to 101.2, no dyspnea, no myalgias, no GI symptoms, more fatigued than normal. • Fully vaccinated • PMH significant for obesity (BMI>99th percentile for age), prediabetes, and mild asthma • Daily medications include metformin 500 mg daily and albuterol inhaler Q4H PRN. Has also been taking Tylenol for fever control.
Clinical decision	• Offer treatment with Paxlovid.
Key points/notes	• She is symptomatic and within the time window for all therapeutics. • She has risk factors for progression to severe disease • Mom accepted treatment for patient. They were advised of potential side effects of treatment and to to continue daily medications and OTC treatment PRN for symptom control. While pediatric patients as a whole are at lower risk than adults, they should still be offered available therapeutic options if they have underlying medical conditions that would put them at higher risk for progression to severe illness.

13 yo M with Lowe Syndrome: Mild COVID

Patient presentation	• 13-year-old male with history of Lowe Syndrome presents to office, positive for Covid-19
Findings/attributes	• Mom reports he is on day 3 of symptoms. Symptoms include significant fatigue, decreased appetite/PO intake relating to sore throat, mild fever of 100.4. • PMH significant for Lowe Syndrome, Fanconi Syndrome and Type 1 Diabetes Mellitus • Not vaccinated • eGFR 32
Clinical decision	• Offer treatment with Bebtelovimab
Key points/notes	• Given patients complex medical history, he is routinely followed by pediatric nephrology and endocrinology • Consulted with patient's nephrologist and pediatric infectious disease • Concern by nephrology that his eGFR had already dropped significantly from baseline (prior eGFR 2 months ago was 48) so felt Paxlovid and Remdesivir were not good options, and therefore patient was set up for Bebtelovimab infusion through local infusion clinic • Paxlovid and Remdesivir are the preferred therapeutic agents in treatment of Covid-19, however Bebtelovimab is an alternate option if clinically appropriate. In this case, consulting with patient's specialty care team was warranted to determine the most appropriate treatment option for this medically complex patient.

Addressing Renal Function when Prescribing Paxlovid

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Northern Light Health

Maine Medical Association

EUA for Paxlovid

- Doseage: 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together twice daily for 5 days
- Dose reduction for moderate renal impairment (eGFR ≥ 30 to < 60 mL/min): 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days
- Paxlovid is not recommended in patients with severe renal impairment (eGFR <30 mL/min)

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

Assessing Risk Factors for CKD if eGFR is unknown

- Increased risk factors include:
  - Age > 65
  - History of AKI
  - Diabetes
  - Poorly controlled HTN
  - Family history CKD
  - Obesity (especially BMI >35), smoking history, frequent/daily NSAID use, and substance use disorders
- National Kidney Foundation (https://www.kidney.org/) has helpful tools/calculators to help clinicians determine risk of chronic kidney disease

59 yo M with no comorbidities: Mild Covid

Patient presentation	• 59 year-old-male patient positive for Covid-19 at walk-in-care drive through site, no local PCP
Findings/attributes	• Reports symptoms started 4 days ago and include congestion, dry cough, mild headache, myalgia, and significant fatigue. Low grade fever of 100.4, reduced with Tylenol. Denies shortness of breath, chest pain/pressure, GI symptoms. • PCP located in FL and records are not available for review; he reports that he generally gets annual physical but otherwise doesn't go to his PCP much, reports he has never been told he has "any issues with his kidneys." • Fully vaccinated with first booster, not second • PMH significant for being overweight (BMI 28). No daily medications. • Denies smoking history, frequent NSAID use, known family history of CKD
Clinical decision	• Offer treatment with Paxlovid.
Key points/notes	• Despite not having access to patient's records, he is generally healthy and has no specific indications to screen for renal disease. • His age puts him at increased risk for progression to severe disease • Delaying treatment to obtain eGFR puts this patient at risk for being outside of treatment window with Paxlovid as he is already on day 4 of symptoms, and it is better to start treatment as early as possible in course of illness. He also does not have any clinic history to indicate that he is at increased risk for CKD - his eGFR is "known or expected to be >60, and he agreed to treatment with Paxlovid.

41 yo F with IgA Nephropathy: Mild Covid

Patient presentation	• 41-year-old F with PMH significant for IgA Nephropathy reports positive home Covid-19 test
Findings/attributes	• Reports symptoms started 4 days ago and include congestion, dry cough, mild headache, myalgia, and significant fatigue. Low grade fever of 100.4, reduced with Tylenol. Denies shortness of breath, chest pain/pressure, GI symptoms. • IgA nephropathy is stable, patient follows with nephrology every 6 months, and last eGFR was obtained ~3 months ago and was 48 mL/min • Fully vaccinated • Daily medications include Lisinopril 20 mg daily, Atorvastatin 20 mg daily
Clinical decision	• Offer treatment with reduced dose Paxlovid.
Key points/notes	• Chronic kidney disease is a risk factor for Covid-19 progression to severe disease and Paxlovid is preferred treatment • There is no indication to repeat eGFR at this time; IgA nephropathy has been stable and last eGFR is well within range of utilizing reduced dose Paxlovid • Patient advised to discontinue statin medication for course of treatment with Paxlovid and to resume regular dose 3 days after completing treatment • Patients with known chronic kidney disease or significant risk factors for chronic kidney disease should be evaluated on a case-by-case basis when deciding to repeat an eGFR. It is also okay to initiate treatment with Paxlovid, obtain an eGFR, and adjust dosing based on results when available.

Specific Drug-Drug Interactions with Paxlovid: Anticoagulants

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Anticoagulants

- Paxlovid, specifically ritonavir, interacts with multiple anticoagulants as they are generally strong CYP3A4 and P-gp inhibitors
- Paxlovid is the first line recommended treatment for Covid-19, and therefore clinicians should try to adjust medications, including many anticoagulants, as ***both mAb and molnupiravir are recommend only for use when ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir are not available, feasible to use, or clinically appropriate***
- The NIH recommends clinicians utilize web-based drug interaction checkers for specific medication interactions and dose adjustment recommendations
  - The Liverpool Covid-19 Drug Interactions website
  - The Ontario COVID-19 Science Advisory Table

Temporarily Withhold Concomitant Medication, If Clinically Appropriate

Withhold these medications during ritonavir-boosted nirmatrelvir treatment and for at least 2–3 days after treatment completion. They may need to be withheld for longer if the patient is elderly or the medication has a long half-life. If withholding is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy.

Anticoagulants

- Rivaroxaban[d]

Adjust Concomitant Medication Dose and Monitor for Adverse Effects

Consult the Liverpool COVID-19 Drug Interactions website or the Ontario COVID-19 Science Advisory Table for specific dosing recommendations.[i] If the dose of the concomitant medication cannot be adjusted, withhold the medication (if clinically appropriate) or use an alternative concomitant medication or COVID-19 therapy.

Anticoagulants

- Apixaban
- Dabigatran
- Edoxaban

Continue Concomitant Medication and Monitor for Adverse Effects

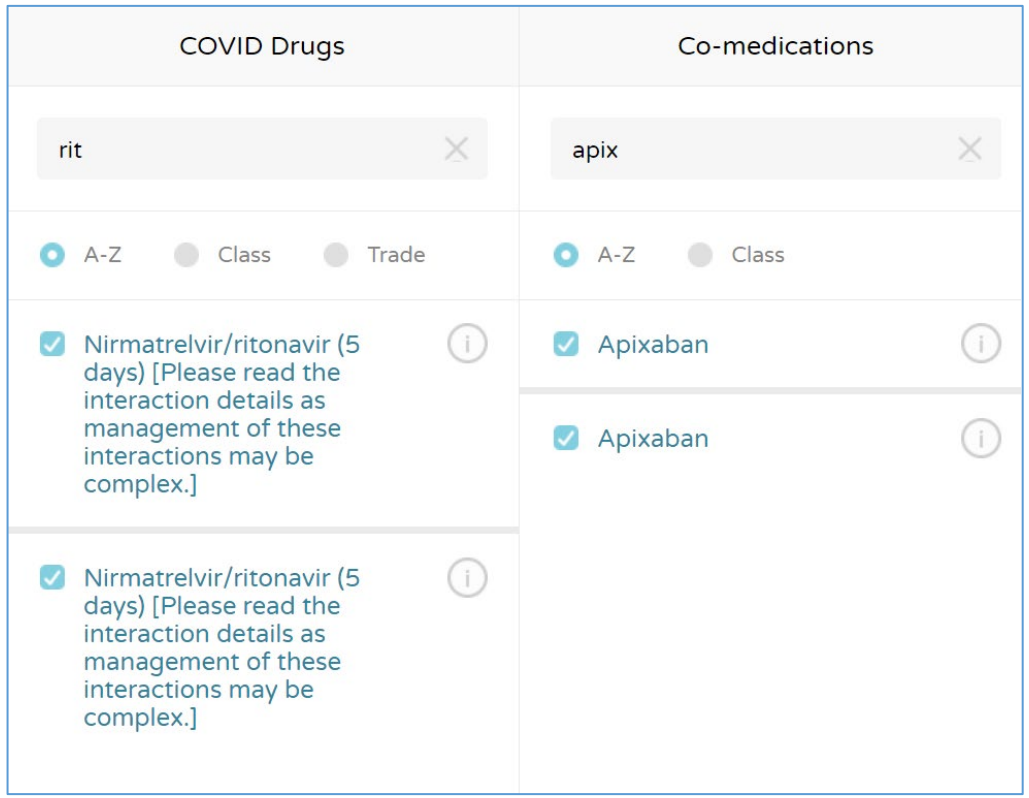
Pre-emptive dose adjustment is not required but may be considered. Educate patients on potential adverse effects. Consult the Liverpool COVID-19 Drug Interactions website or the Ontario COVID-19 Science Advisory Table for monitoring guidance and dose adjustment information if needed.[i]

Anticoagulants

- Warfarin

69 yo M on chronic anticoagulation: Mild COVID

Patient presentation	• 69-year-old M reports positive home Covid-19 test to PCP
Findings/attributes	• Day 4 of symptoms. Started with sore throat and nasal congestion. Now sore throat, nasal congestion, non-productive cough, no fever, no dyspnea, no myalgias, no GI symptoms, more fatigued than normal. • Fully vaccinated and boosted • PMH significant for long-standing rate controlled atrial fibrillation, currently anticoagulated on apixiban 5 mg BID for 5+ years. No history of blood clots. He is also on carvedilol 12.5 mg BID and atorvastatin 40 mg daily. • Most recent eGFR >60, 2 months ago at cardiologist
Clinical decision	• Offer treatment with Paxlovid, adjust apixiban and other medications as indicated
Key points/notes	• He is symptomatic and within the time window for all therapeutics. He has risk factors for progression to severe disease. • Paxlovid treatment was offered to patient. He was advised to halve his dose of apixiban for full course of treatment and resume normal dosing 3 days after completion of treatment. He was advised to discontinue atorvastatin 40 mg for full course of treatment and to resume medication 3 days after completion of treatment. He was made aware of slightly increased risk of bleeding and to seek prompt medical attention with any concerns or with any falls. • The risks and benefits and indications for anticoagulation should be thoroughly examined on a case-by-case basis for each patient. After thorough review of specific anticoagulant-Paxlovid drug-drug interactions and patients individual risk factors, some anticoagulants can be adjusted to allow for treatment of Covid-19 with Paxlovid.



option to use apixaban at a reduced dose (i.e., 2.5 mg) if needed. Of interest, no adverse outcomes were reported in six HIV infected patients treated with a reduced dose of apixaban (2.5 mg twice daily) while on ritonavir boosted regimens suggesting that a reduced dose of apixaban could be used with nirmatrelvir/ritonavir. If nirmatrelvir/ritonavir treatment is needed, consider adjusting apixaban dosage according to risk, indication and current dose. For treatment of atrial fibrillation with standard apixaban dose (i.e., 5 mg twice daily), reduce apixaban to 2.5 mg twice daily. For treatment of atrial fibrillation

Managing Paxlovid Drug-Drug Interactions

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Matthew Marston, PharmD, MBA, BCPS, BCOP, Northern Light Health
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Take 3 tablets at
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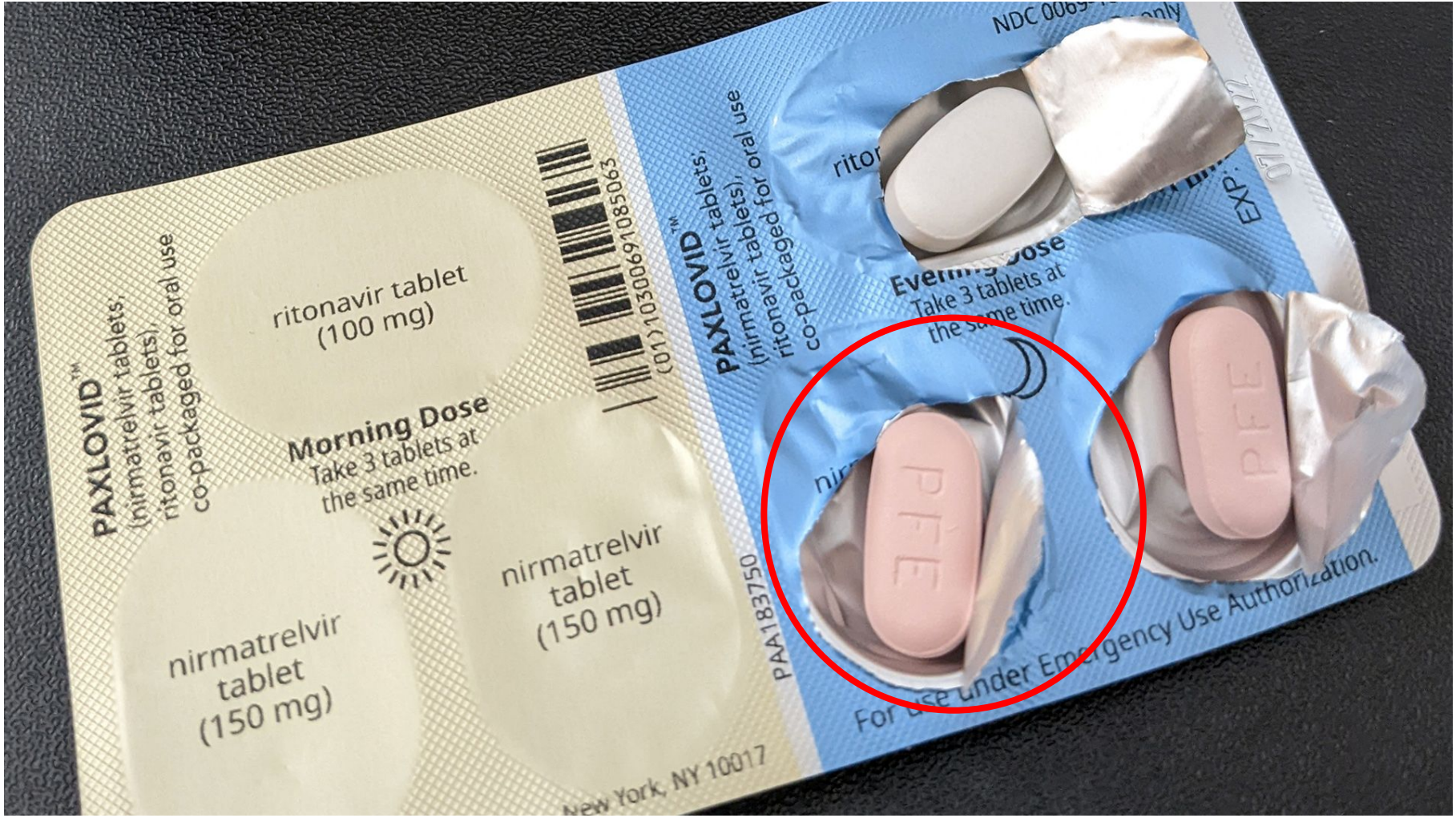
For use under Emergency Use Authorization.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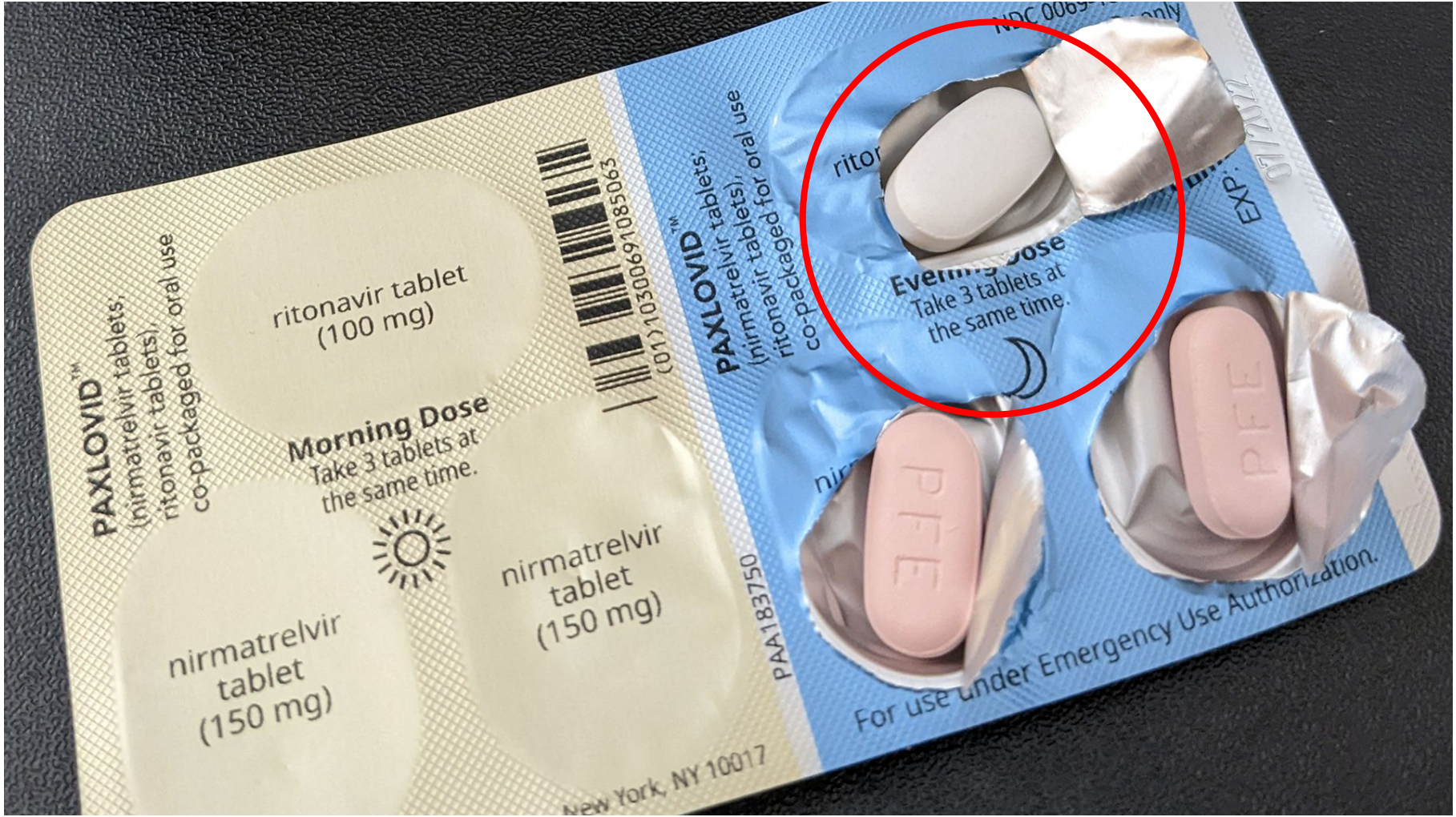
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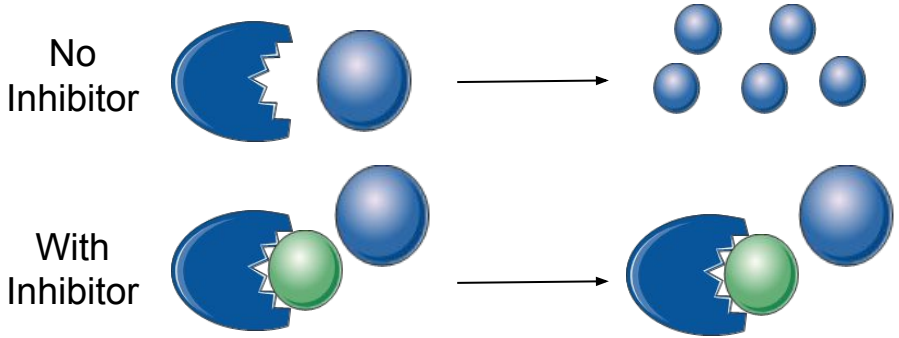
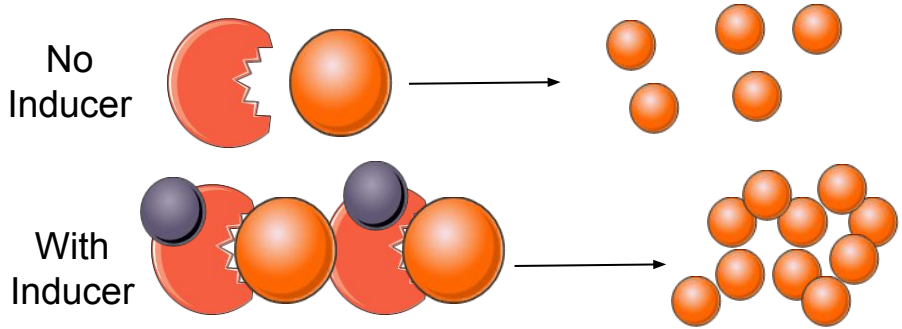
Cytochrome (CYP) P450 Enzymes & Metabolism

- CYP P450 enzymes are essential components of drug metabolism
- Enzyme inhibition or induction may lead to altered metabolism of target drug

Inhibition	Induction
Substance impedes enzymes ability to degrade target drug molecule	Increases number of enzymes available to degrade target drug molecule
Resolves when offending substance removed or cleared (dependent on half-life)	Onset and offset correspond to synthesis and degradation of enzymes (5 - 7 days)



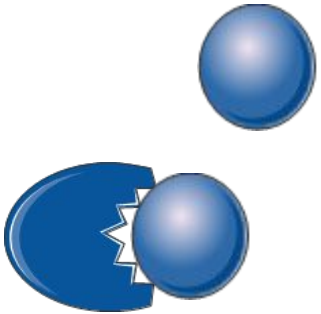


Park BK. *Clin Pharmcokinet.* 1981;6:1-24

Images partly generated using Servier Medical Art, provided by Servier

CYP P450 Inhibitors and Substrates

- Paxlovid® formulated with 2 antivirals: nirmatrelvir + ritonavir



Salmeterol

No Ritonavir

Selected CYP3A4 Substrates	
Amiodarone	Rivaroxaban
Amlodipine	Salmeterol
Clopidogrel	Statins
Corticosteroids	Sildenafil
Digoxin	Tacrolimus
Quetiapine	Trazodone

Paxlovid [package insert]. New York, NY. Pfizer Inc;2022

Interaction viewed using Lexicomp Drug Interactions Database: Lexicomp Online. Waltham, MA: UpToDate, Inc.; https://online.lexi.com. Accessed July 7, 2022.

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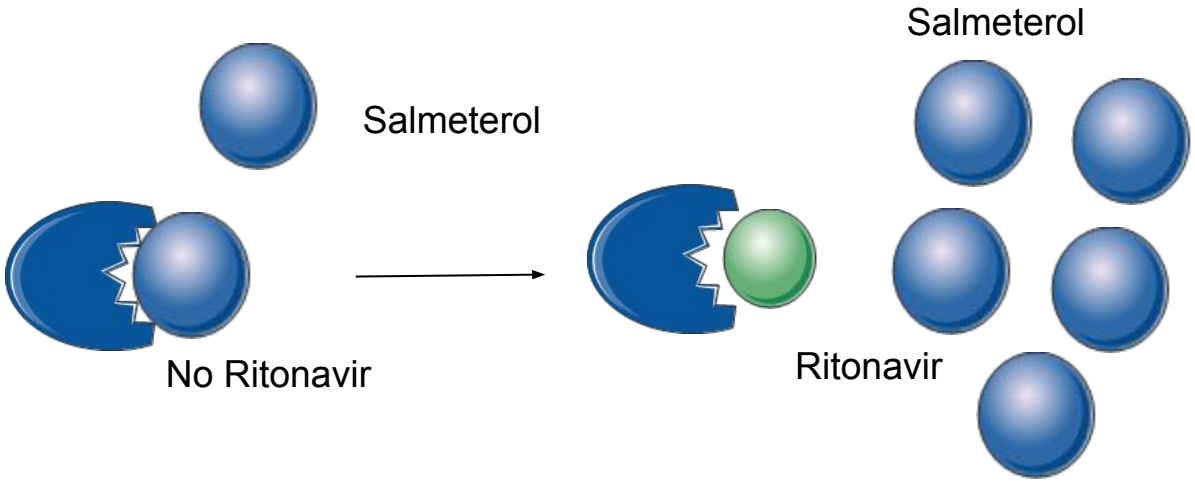

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Amiodarone	Rivaroxaban
Amlodipine	Salmeterol
Clopidogrel	Statins
Corticosteroids	Sildenafil
Digoxin	Tacrolimus
Quetiapine	Trazodone

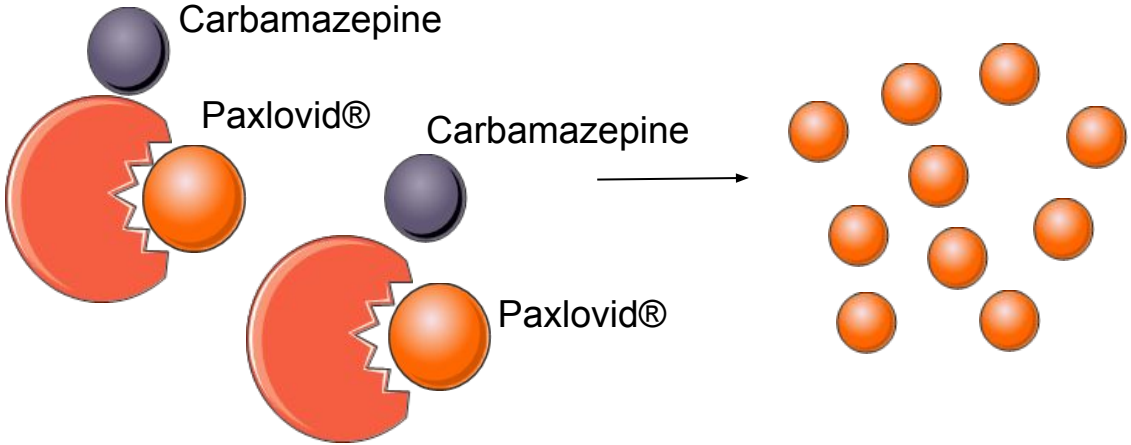
Presence of ritonavir results in a **15-fold increase** in exposure to salmeterol

Paxlovid [package insert]. New York, NY. Pfizer Inc;2022

Interaction viewed using Lexicomp Drug Interactions Database: Lexicomp Online. Waltham, MA: UpToDate, Inc.; https://online.lexi.com. Accessed July 7, 2022.

CYP P450 Inducers

- Components of Paxlovid® (nirmatrelvir and ritonavir) **are also substrates of CYP3A4**



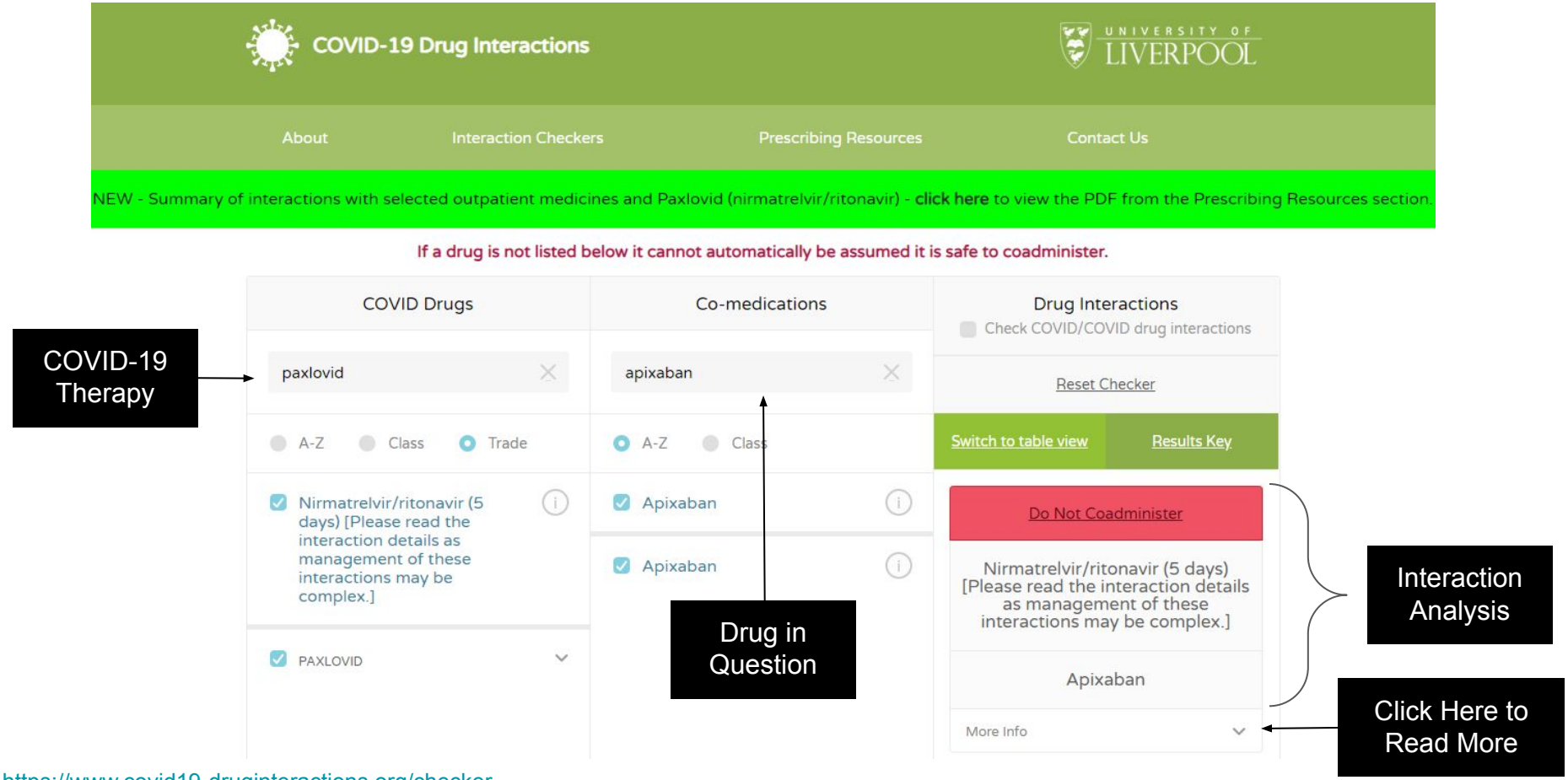
Strong CYP3A4 Inducers
Carbamazepine
Phenobarbital
Phenytoin
Rifampin
St. John's Wort

Co-administration with carbamazepine results in a **50% decrease** in Paxlovid® exposure

Paxlovid [package insert]. New York, NY. Pfizer Inc;2022

Interaction viewed using Lexicomp Drug Interactions Database: Lexicomp Online. Waltham, MA: UpToDate, Inc.; https://online.lexi.com. Accessed July 7, 2022.

Drug-Interaction Resources: **Liverpool COVID-19 Interaction Checker**



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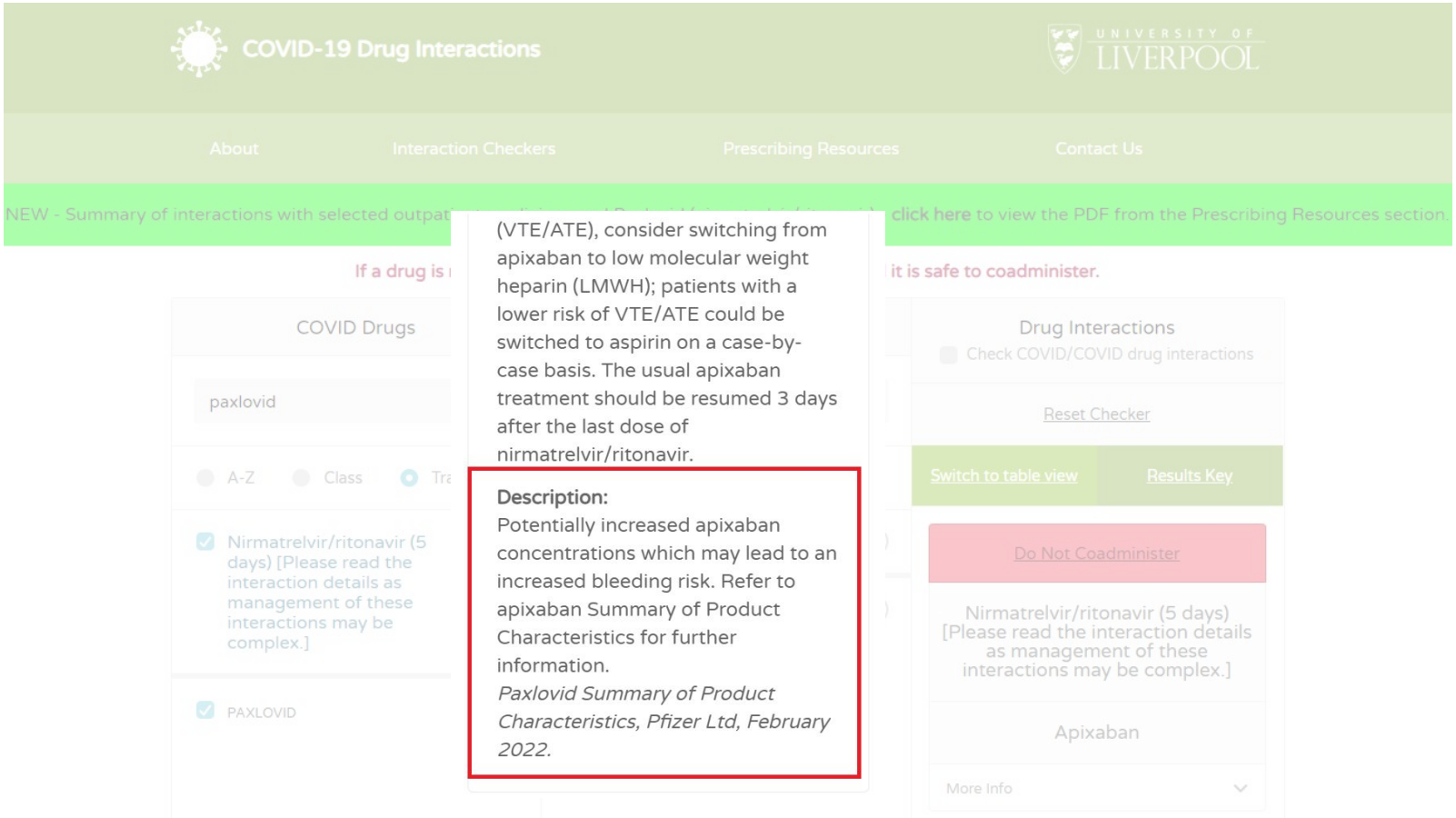

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Drug-Interaction Resources: **IDSA Documents for Clinicians**

- Contains interaction analyses on ClinCalc's Top 200 Prescribed Medications in the United States (2019)

Management of Drug Interactions With Nirmatrelvir/Ritonavir (Paxlovid®): Resource for Clinicians

IDSA
Infectious Diseases Society of America

IDSA COVID-19 TREATMENT AND MANAGEMENT GUIDELINE PANEL ON BEHALF OF THE INFECTIOUS DISEASES SOCIETY OF AMERICA

Concomitant Medication	Nirmatrelvir/ Ritonavir Effect on Drug Level	Possible Effect	Recommendation During Nirmatrelvir/Ritonavir Treatment
Statins (HMG-CoA reductase inhibitors)	↑ **most statins**	Increased toxicity	Hold statins during nirmatrelvir/ritonavir course and for 5 days after

https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/management-of-drug-interactions-with-nirmatrelvirritonavir-paxlovid/

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Management of Common Interactions

Drug	Effect	Recommendation
Statins	↑ statin exposure	- HOLD statin 12 hrs prior to Paxlovid - Hold until 3-days after completion of Paxlovid
Ethinyl Estradiol Contraceptives	↓ ethinyl estradiol concentrations may lead to contraceptive failure	Add additional **non-hormonal contraceptive** method until the following menstrual cycle
Fluticasone/budesonide (inhaled/intranasal steroids)	↑ steroid exposure leading to significant (up to 90%) reduction in serum cortisol exposure	- Hold steroid (especially intranasal fluticasone) when possible - Counsel patient to self-monitor for signs of adrenal insufficiency
Salmeterol (inhaled beta-agonist)	↑ systemic salmeterol exposure 15-fold Increased risk of cardiac events (QT prolongation, palpitations, sinus tachycardia) have been reported	- If inhaler can be held, hold until 3 days following completion of Paxlovid - If inhaler cannot be held, use alternative COVID-19 therapy
Trazodone	↑ trazodone exposure by up to 2-fold	- Consider holding PRN trazodone until 3 days after completion of Paxlovid - Reduce dose if possible - Counsel patient to self-monitor for increased drowsiness, sedation

Interactions were viewed using Lexicomp Drug Interactions Database: Lexicomp Online. Waltham, MA: UpToDate, Inc.; https://online.lexi.com. Accessed July 6, 2022.

Management of Common Interactions

Drug	Effect	Recommendation
Statins	↑ statin exposure	- HOLD statin 12 hrs prior to Paxlovid - Hold until 3-days after completion of Paxlovid
Ethinyl Estradiol Contraceptives	↓ ethinyl estradiol concentrations may lead to contraceptive failure	Add additional **non-hormonal contraceptive** method until the following menstrual cycle
Fluticasone/budesonide (inhaled/intranasal steroids)	↑ steroid exposure leading to significant (up to 90%) reduction in serum cortisol exposure	- Hold steroid (especially intranasal fluticasone) when possible - Counsel patient to self-monitor for signs of adrenal insufficiency
Salmeterol (inhaled beta-agonist)	↑ systemic salmeterol exposure 15-fold Increased risk of cardiac events (QT prolongation, palpitations, sinus tachycardia) have been reported	- If inhaler can be held, hold until 3 days following completion of Paxlovid - If inhaler cannot be held, use alternative COVID-19 therapy
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DDI Management Summary

		Examples
Strong CYP3A4 *Inducers*	• **<u>Do not use Paxlovid</u>** ○ Do not attempt to hold offending med, since induction effect will not dissipate for several days to weeks	Phenytoin Carbamazepine Phenobarbital Rifamycins St John's Wort
High Risk of Harm (Contraindicated)	• **HOLD** home med, if possible ○ Hold until 3-5 days post Paxlovid completion • If med cannot be held, use **<u>alternative</u>** COVID-19 therapy	Salmeterol Inhaler Statins
Interactions with Potential Harm	• **HOLD** home med, if possible ○ Hold until 3-5 days post Paxlovid completion • **Reduce dose:** package insert, drug interaction checkers, or pharmacists for help	Apixaban Quetiapine Oxycodone
Interactions with Little Clinical Impact	Educate patient to self-monitor for signs of toxicity	Amlodipine Levothyroxine Pantoprazole Sertraline

DDI Management Summary

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Strong CYP3A4 *Inducers*	• **<u>Do not use Paxlovid</u>** ○ Do not attempt to hold offending med, since induction effect will not dissipate for several days to weeks	Phenytoin Carbamazepine Phenobarbital Rifamycins St John's Wort
High Risk of Harm (Contraindicated)	• **HOLD** home med, if possible ○ Hold until 3-5 days post Paxlovid completion • If med cannot be held, use **<u>alternative</u>** COVID-19 therapy	Salmeterol Inhaler Statins
Interactions with Potential Harm	• **HOLD** home med, if possible ○ Hold until 3-5 days post Paxlovid completion • **Reduce dose:** package insert, drug interaction checkers, or pharmacists for help	Apixaban Quetiapine Oxycodone
Interactions with Little Clinical Impact	Educate patient to self-monitor for signs of toxicity	Amlodipine Levothyroxine Pantoprazole Sertraline

Additional Resources and Considerations

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- Information may vary across resources, check multiple sources
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Severe COVID-19

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Severe COVID

Patient presentation	• 43-year-old female presents to COVID One Stop Shop, positive in-clinic rapid test
Findings/attributes	• Symptom day 6, new exertional dyspnea, productive cough with orthopnea • BMI 49, current smoker, OSA on CPAP • Primary mRNA vaccine series completed, no booster • Room air SpO_2 90-92%
Clinical decision	• Emergency Department evaluation indicated
Key points/notes	• She has progressed to severe COVID illness • COVID-19 therapeutics for mild-moderate illness are not indicated

Lagevrio Use Case Scenario

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Lagevrio use case scenario

Patient presentation	• 52-year-old male, institutional setting, positive rapid test
Findings/attributes	• Day 1 of symptoms, fever and cough • Contraindications to Paxlovid • Bebtelovimab administration barriers • Primary mRNA series complete, first and second booster complete
Clinical decision	• Lagevrio (molnupiravir) indicated
Key points/notes	• Lagevrio is best option in some situations • For use only when preferred therapies are unavailable, not feasible or clinically inappropriate • Examples may include transportation barriers, non-availability of alternate therapies