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AAP-OC

American Academy of Pediatrics
Orange County Chapter
INCORPORATED IN CALIFORNIA

Review of COVID Therapeutics

Regina Chinsio-Kwong, DO OCHCA Health Officer

May 25, 2022

Disclosure

I personally do not have a financial relationship or interest (currently or within the past 24 months) with any proprietary entity producing health care goods or services consumed by or used on patients related to the content of this CME.

I do however have an immediate family member with a few shares of Merck & Co.

I do not intend to discuss an unapproved/investigative use of a commercial product/device.

Special Thanks

- CDPH staff
- American Academy of Pediatrics- OC Chapter
- Orange County Medical Association
- California Academy of Family Physician
- Riverside County and Yuba/Sutter County Health Officers

Learning Objectives

- Current County COVID status
- COVID therapeutics (focus on outpatient therapeutic options)
  - Evusheld
  - Oral Antivirals

- Effective outpatient treatment options are more widely available for those with mild to moderate COVID-19 and should be offered to high-risk patients if they meet criteria

Current State

Linear Adjusted Case Rate per 100K: 13.7

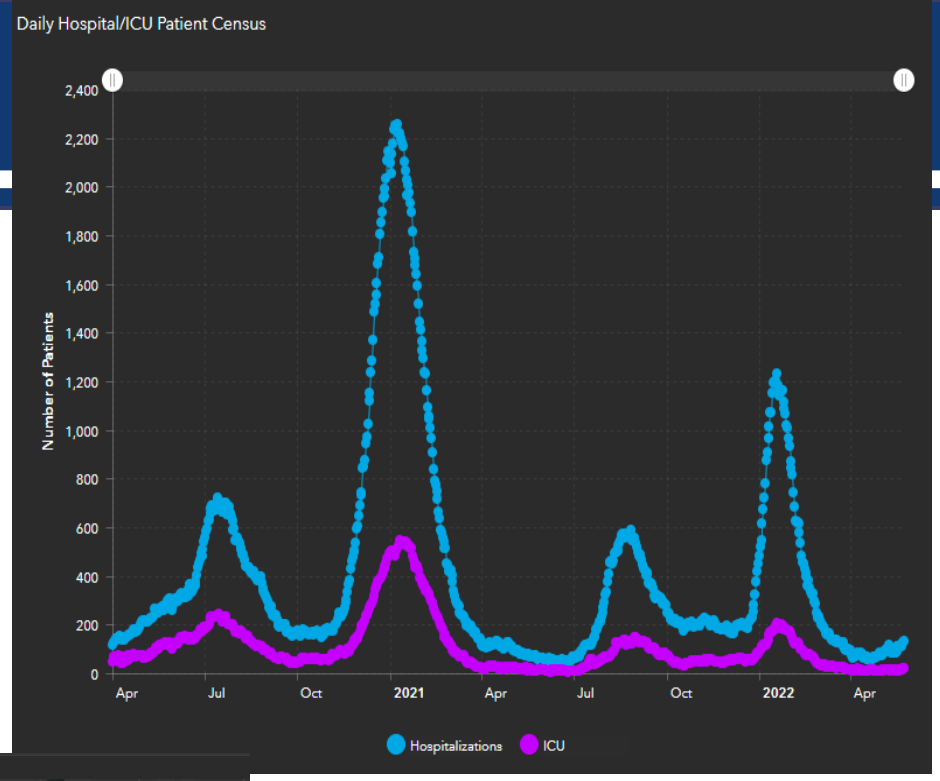
Unadjusted Daily Case rate per 100K: 18.3

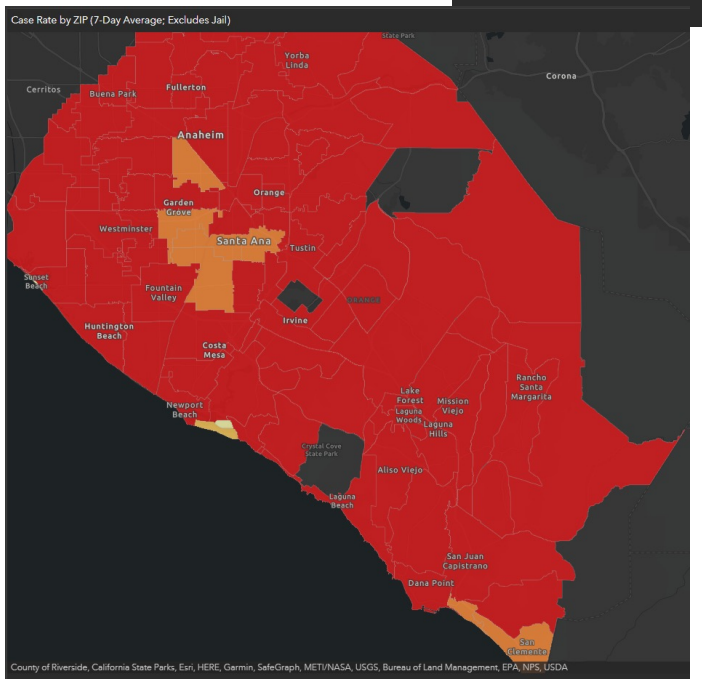
Case Positivity: 5.5% (2.4% in HPI 1)

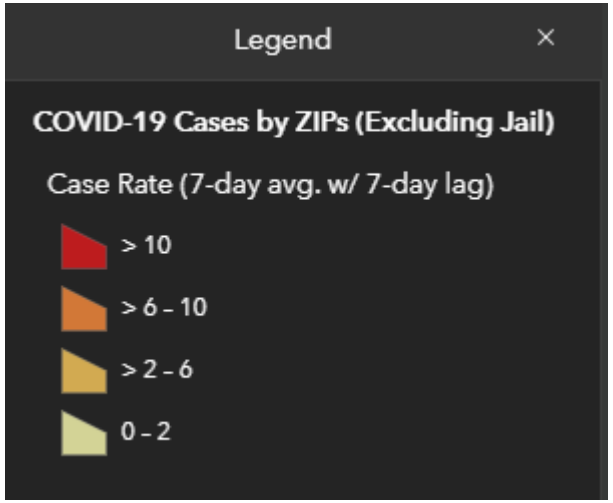
 # hospitalized: 131

 # in ICU: 20

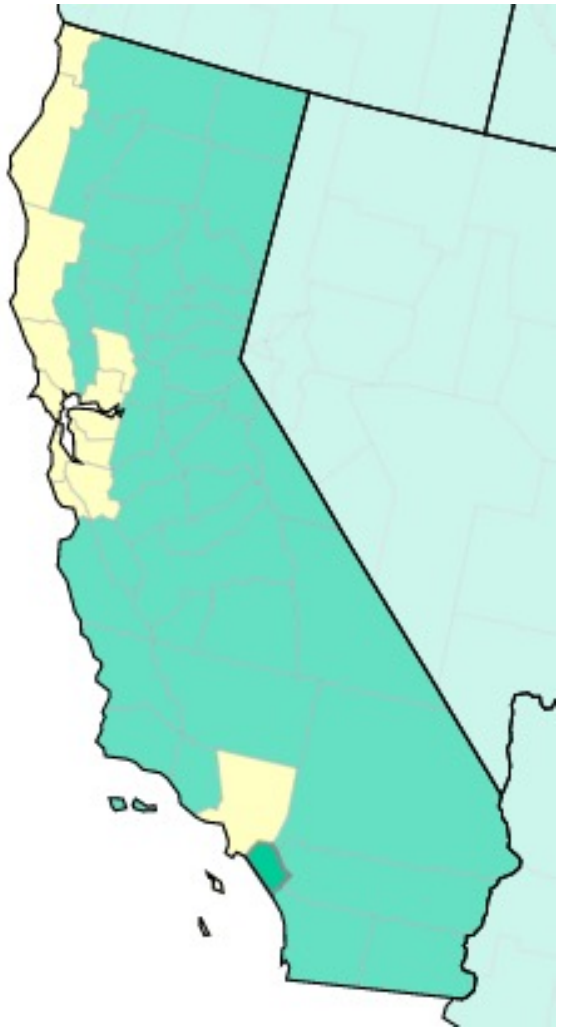
Cumulative # Deaths to date: 7030







CDC- Community levels and Transmission levels



Orange County, California

State Health Department

COVID-19 Community Level

Low

Recommended actions based on current level

Stay up to date with COVID-19 vaccines. Get tested if you have symptoms. Wear a mask if you have symptoms, a positive test, or exposure to someone with COVID-19. Wear a mask on public transportation. You may choose to wear a mask at any time as an additional precaution to protect yourself and others.

Weekly Metrics Used to Determine the COVID-19 Community Level

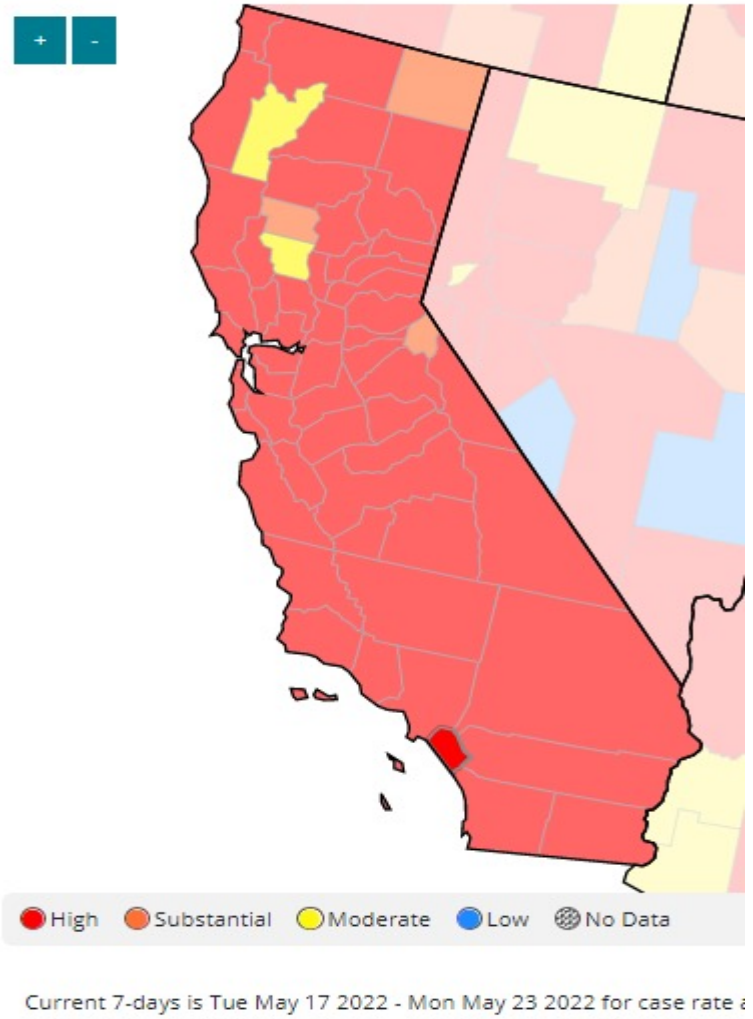
Case Rate per 100,000 population	138.24
New COVID-19 admissions per 100,000 population	3.7
% Staffed inpatient beds in use by patients with confirmed COVID-19	1.8%

How are COVID-19 Community Levels calculated?

Note: The COVID-19 Community Level and associated metrics presented above are updated weekly on Thursday and may differ from the values for the same metrics presented below, which are updated daily.

COVID-19 Community Levels – Use the Highest Level that Applies to Your Community

New COVID-19 Cases Per 100,000 people in the past 7 days	Indicators	Low	Medium	High
Fewer than 200	New COVID-19 admissions per 100,000 population (7-day total)	<10.0	10.0-19.9	≥20.0
	Percent of staffed inpatient beds occupied by COVID-19 patients (7-day average)	<10.0%	10.0-14.9%	≥15.0%
200 or more	New COVID-19 admissions per 100,000 population (7-day total)	NA	<10.0	≥10.0
	Percent of staffed inpatient beds occupied by COVID-19 patients (7-day average)	NA	<10.0%	≥10.0%

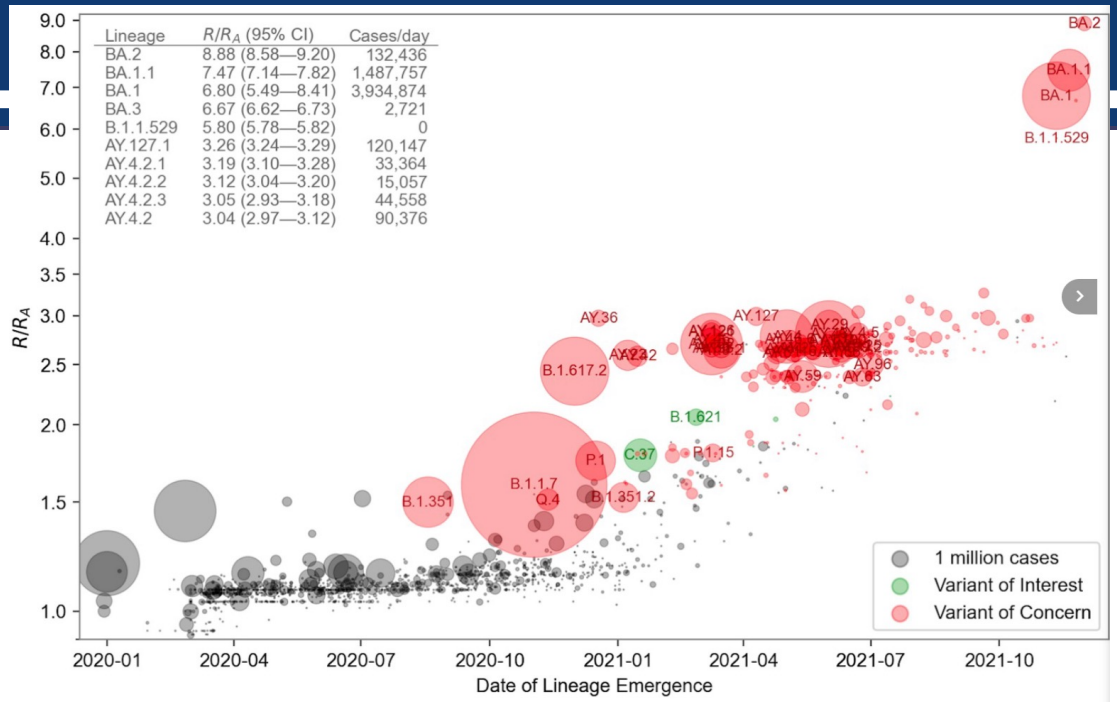


Current 7-days is Tue May 17 2022 - Mon May 23 2022 for case rate a

It's time to layer up on protection- regardless of vaccination status when in crowded areas/indoors!

Omicron

- **More transmissible than prior variants-**
  - Variants today have increased fitness compared to earlier in the pandemic!
- **Still can cause severe illness- but more commonly in unvaccinated, immunocompromised, frail individuals**
- **Vaccines offer less protection to Omicron vs previous variants earlier in pandemic due to some immune escape**
- **Susceptibility to monoclonal antibodies appears to be lower for Omicron compared to Delta**
- **Bebtelovimab is presumed effective against Omicron Variants**
- **Evusheld effective is presumed effective against Omicron Variants**



Analysis of 6.4 million SARS-CoV-2 genomes identifies mutations associated with fitness

FRITZ OBERMEYER, MARTIN JANKOWIAK, NIKOLAOS BARKAS, STEPHEN F. SCHAFFNER, JESSE D. PYLE, LEONID YURKOVETSKIY, MATTEO BOSSO, DANIEL J. PARK, MEHRTASH BABADI, [...] JACOB E. LEMIEUX +4 authors Authors Info & Affiliations

SCIENCE · 24 May 2022 · First Release · DOI: 10.1126/science.abm1208

https://www.science.org/doi/10.1126/science.abm1208

COVID Prevention- Vaccines/Therapeutics

Vaccines

- **Pfizer (mRNA) – 5+**
  - EUA for 5+ Primary series and for first Booster 5+
    - EUA 2nd booster: Moderately-Severely immunocompromised age 12-49 y/o or age 50+ *Should* get a 2nd booster
  - FDA Approved for 16+ Primary Series
- **Moderna (mRNA) 18+**
  - EUA for 18+ Primary Series and Booster
    - EUA 2nd booster: Moderately-Severely immunocompromised age 18-49 y/o or age 50+ *Should* get a 2nd booster
- **J&J – 18+**
  - EUA for 18+ Primary Series
    - EUA booster: anyone 18+ who completed 1st dose advised to get booster with mRNA
    - EUA Moderately-Severely Immunocompromised: advised to get 2nd dose with mRNA, booster with mRNA

Pre-Exposure Prophylaxis (PrEP)

- **Tixagevimab + Cilgavimab (Evusheld)- Long-Acting Monoclonal Antibody (IM injection)**
  - Age 12+ and > 40kg

COVID-19 Vaccine Timing

COVID-19 Vaccine Timing by Age

Vaccinate ALL 58

Routine Schedule

Age	Vaccine	Primary Doses	1st Booster Dose	2nd Booster Dose
5-11	Pfizer–Pediatric (5-11)	1st Dose → 3 weeks → 2nd Dose → ≥5 months	Booster	
12+	Pfizer/ Comirnaty (12+)	1st Dose → 3 weeks (8 weeks for some people^) → 2nd Dose → ≥5 months	1st Booster **Ages 12-17:** Pfizer **18+:** Moderna/Pfizer (mRNA preferred) or J&J*	≥4 months → 2nd Booster **Ages 50+:** Moderna/Pfizer **18-49:** Not currently recommended**
18+	Moderna/ Spikevax	1st Dose → 4 weeks (8 weeks for some people^) → 2nd Dose → ≥5 months		
18+	Johnson & Johnson Pfizer/Moderna preferred*	1st Dose → ≥2 months		

^ An 8-week interval may be preferable for some people, especially for males 12-39 years.
* Although use of mRNA COVID-19 vaccines is preferred, the Janssen vaccine may be offered in some situations.
** People who received J&J for their primary and first booster dose may consider receiving an mRNA vaccine as a second booster.

View Interim Clinical Considerations for Use of COVID-19 Vaccines for details. Schedule is subject to change.

California COVID-19 Vaccination Program IMM-1396 (5/20/22)

https://eziz.org/assets/docs/COVID19/IMM-1396.pdf

Note Timing Intervals Differ!

Schedule if Moderately or Severely Immunocompromised

Age	Vaccine	Primary Doses	1st Booster Dose	2nd Booster Dose
5-11	Pfizer–Pediatric (5-11)	1st Dose → 3 weeks → 2nd Dose → ≥4 weeks → 3rd Dose → ≥3 months	Booster	
12+	Pfizer/ Comirnaty (12+)	1st Dose → 3 weeks → 2nd Dose → ≥4 weeks → 3rd Dose → ≥3 months	1st Booster **Ages 12-17:** Pfizer **18+:** Pfizer/ Moderna (mRNA preferred) or J&J*	≥4 months → 2nd Booster **Ages 12-17:** Pfizer **18+:** Moderna/ Pfizer 12+ moderately/severely immunocompromised should get 2nd booster
18+	Moderna/ Spikevax	1st Dose → 4 weeks → 2nd Dose → ≥4 weeks → 3rd Dose → ≥3 months		
18+	Johnson & Johnson Pfizer/Moderna preferred*	1st Dose → 4 weeks → 2nd Dose of Moderna or Pfizer → ≥2 months		

*Although use of mRNA COVID-19 vaccines is preferred, the Janssen vaccine may be offered in some situations.

View COVID-19 Vaccines for Moderately or Severely Immunocompromised People for details. Schedule is subject to change.

Tixagevimab/Cilgavimab – (Evusheld) PrEP

Manufacturer	AstraZeneca
FDA EUA Date	2/24/22
Drug Type/Class/MOA	Monoclonal Antibody (mAb) mAb against conserved epitope of spike protein; blocks viral entry
Reported efficacy data	77% reduction in developing symptomatic COVID-19
Indication	Pre-Exposure Prophylaxis for those with moderate to severe immunocompromise or for those who any EUA or approved vaccine is not recommended. Individual should not currently be infected or have recent exposure
Age/weight requirement	12+ (minimum 40 kg or 88 lb)
Rx window	Pre-Exposure Period for eligible individual
Duration of therapy	**1 dose**
Testing Requirements **And lab considerations**	none
History requirements **Family planning**	Not specified

Dose	300 mg of Tixagevimab (100 mg/mL) and 300 mg of Cilgavimab (100 mg/mL) via two separate 3.0 mL consecutive intramuscular (IM) injections of each product. *Patients who received previously (150 mg of Tixagevimab and 150 mg of Cilgavimab) should receive a second dose (150 mg of Tixagevimab and 150 mg of Cilgavimab) as soon as possible. The SARS-CoV-2 variants circulating in the US when Evusheld may need to be re-dosed are not known at this time, therefore, repeat dosing recommendations cannot be made.* **Dosing for Special Population:** **Pediatric patients at least 12 years or older**, and weighing at least 40 kg: no dosage adjustment **Pregnancy or Lactation** - No dosage adjustment **Geriatrics**: No dosage adjustment **Renal:** No dosage adjustment **Hepatic:** Not specified
How supplied	One carton has Two vials - 150mg/1.5 ml Tixagevimab - 150mg/1.5 ml Cilgavimab
Administration details	Administer the IM injections at different injections sites (preferably one in each gluteal muscle, one after the other) For 300mg Tixagevimab and 300 mg Cilgavimab dose- ensure that the administration sites are appropriate for the volume (3ml per injection) **Monitor for 1 hour** after injection for hypersensitivity
Adverse Events (if from clinical trials, incidence ≥ 1%)	Injection site reactions 1%: one case of anaphylaxis in clinical trial Headache 6%, fatigue 4%, cough 3%, insomnia 1%, dizziness 1% Injection site reaction 1% Cardiac serious adverse events: 0.6% vs 2% in Evusheld and placebo groups respectively

Potential Drug-Drug Interactions	Unlikely
Renal Dose Adjustment	None
Hepatic Dose Adjustment	None
Contraindications	Previous severe hypersensitivity reactions, including anaphylaxis to any components of Evusheld
Warnings/drug interactions	Monitor for hypersensitivity
Special Populations	Insufficient data in pregnancy or breastfeeding.
cost	$200 administration fee

How to get access of Evusheld for eligible patients

Kaiser

- Fax- monitored M-F- once received, nurse will contact patient to schedule appt

UCI

- **Chao Cancer Center, Orange**
  - Schedule with cancer provider

Providence

- **St. Joseph-**
  - Center for Cancer Prevention and Treatment Infusion Center
- **Mission Hospital**
  - Leonard Cancer Center
  - Mission Heritage Antibiotic Infusion Center
  - By referral only to established criteria

CHOC

- Provider should email to request

Hoag

- By referral from Hoag providers

City of Hope

- By referral from City of Hope Providers

Treating Mild-Moderate COVID-19- Outpatient

Why Treat Mild-Moderate COVID-19?

- Reduce risk of severe illness- hospitalization/death

1) **Verify SARS-CoV-2 infection (antigen/PCR)**
2) **Verify days from initial onset of symptoms**
3) **Is the patient at high risk for developing severe illness?**
4) **Age**
5) **Cautions-**
    1) If considering Paxlovid-
        Kidney: Does patient have renal insufficiency (eGFR < 30)?
        Liver – Severe hepatic impairment- Child-Pugh C?
        Medication Interactions?
    2) If considering Molnupiravir
        Is the patient potentially pregnant?

What is Mild to Moderate COVID-19 Illness?

Mild Illness	Moderate Illness
Absence of Viral Pneumonia & hypoxemia	+ Viral Pneumonia but without hypoxemia
Individuals who have any of the various signs and symptoms of COVID-19 (fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging	Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation ($SpO2$) $\geq$ 94% on room air at sea level.

https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/

Who is at High Risk for Severe COVID outcomes?

Age is the strongest risk factor for severe COVID-19 outcomes, people age 65+ accounted for 81% of US COVID-19 related deaths in 2020

- Cancer
- Chronic kidney disease
- Chronic lung disease
  - Interstitial lung disease, Pulmonary embolism, Pulmonary HTN, Bronchiectasis, COPD
  - Moderate-Severe Asthma
- Chronic liver disease
  - cirrhosis, non-alcoholic fatty liver disease, alcoholic liver disease, autoimmune hepatitis
- Cystic fibrosis
- Primary immunodeficiencies
- Solid Organ or hematopoietic cell transplantation
- Tuberculosis
- HIV
- Use of corticosteroids or other immunosuppressive medications
- Diabetes- type 1 or 2
- Heart conditions (HF, CAD, Cardiomyopathies, congenital heart disease)
- Cerebrovascular disease
- Neurologic condition limited to dementia
- Disabilities (ADHD, Cerebral palsy, congenital malformations (birth defects), intellectual and developmental disabilities, learning disabilities, spinal cord injury
- Mental health disorders (mood disorder including depression, schizophrenia spectrum disorder)
- Sickle Cell Anemia/Thalassemia
- Pregnancy, recent pregnancy
- Smoking- Current/former
- Obesity > 30
- Physical Inactivity

**race/ethnicity, and socioeconomic or behavioral factors

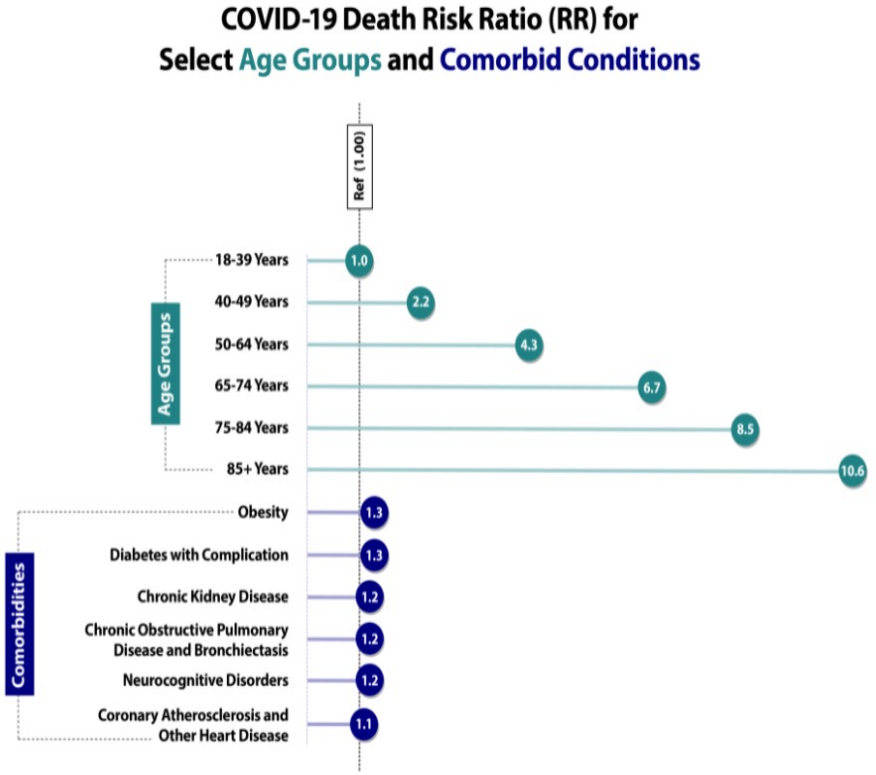
https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

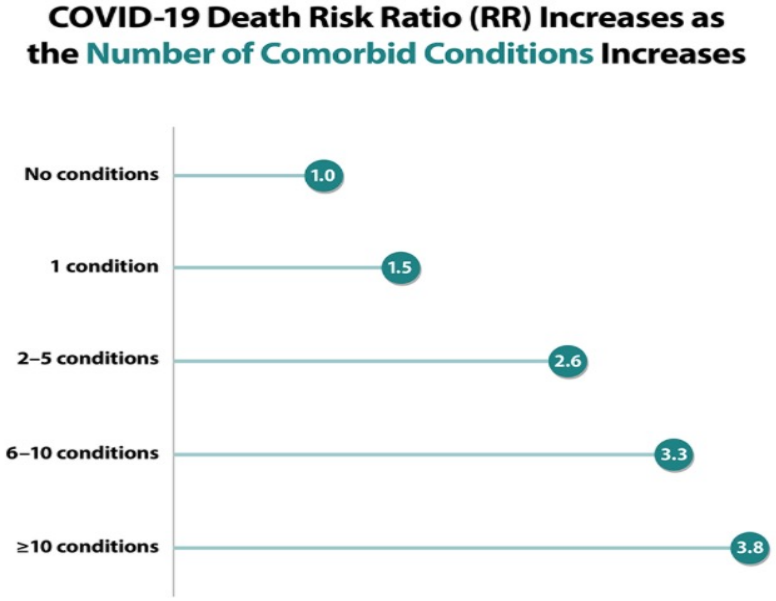
Other details on risks

2. **Suggestive higher risk** for severe COVID-19 outcomes is defined as an underlying medical condition or risk factor that neither has a published meta-analysis or systematic review nor completed the CDC systematic review process. The evidence is supported by mostly cohort, case-control, or cross-sectional studies. (Systematic reviews are available for some conditions for children with underlying conditions.)
   - Children with certain underlying conditions
   - Overweight (BMI ≥25 kg/m^2, but <30 kg/m^2)
   - Sickle cell disease
   - Substance use disorders
   - Thalassemia
3. **Mixed evidence** is defined as an underlying medical condition or risk factor that has a published meta-analysis or systematic review or completing the CDC systematic review process. The meta-analysis or systematic review is inconclusive, either because the aggregated data on the association between an underlying condition and severe COVID-19 outcomes are inconsistent in direction or there are insufficient data (or limited) on the association between an underlying conditions and severe COVID-19 outcomes.
   - Alpha 1 antitrypsin deficiency
   - Asthma
   - Bronchopulmonary dysplasia
   - Hepatitis B
   - Hepatitis C
   - Hypertension*

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

https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html#anchor_1644597791955





Links for identifying Higher Risk individuals

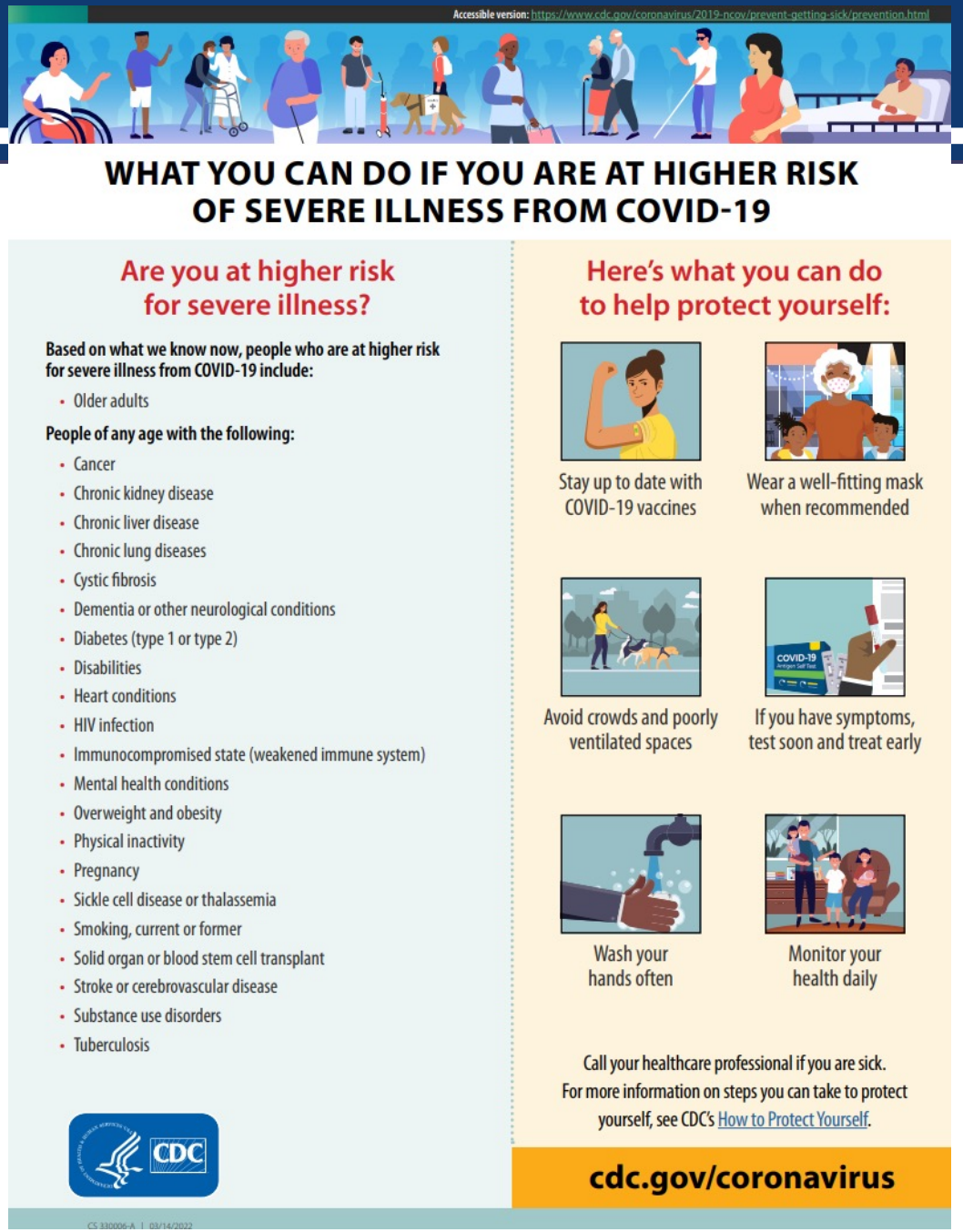
Sites describing those at higher risk

https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/underlying-evidence-table.html

CDC Patient handout:

https://www.cdc.gov/coronavirus/2019-ncov/downloads/COVID19-What-You-Can-Do-High-Risk.pdf



Accessible version: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html

WHAT YOU CAN DO IF YOU ARE AT HIGHER RISK OF SEVERE ILLNESS FROM COVID-19

Are you at higher risk for severe illness?

Based on what we know now, people who are at higher risk for severe illness from COVID-19 include:

- Older adults

People of any age with the following:

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

Here's what you can do to help protect yourself:

Stay up to date with COVID-19 vaccines

Wear a well-fitting mask when recommended

Avoid crowds and poorly ventilated spaces

If you have symptoms, test soon and treat early

Wash your hands often

Monitor your health daily

Call your healthcare professional if you are sick.
For more information on steps you can take to protect yourself, see CDC's How to Protect Yourself.

cdc.gov/coronavirus

CS 330006-A | 03/14/2022

Treatment in outpatient setting for Mild-Moderate COVID-19 illness
NIH guidance

- Clinical Management Summary (4/8/22)

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)**.

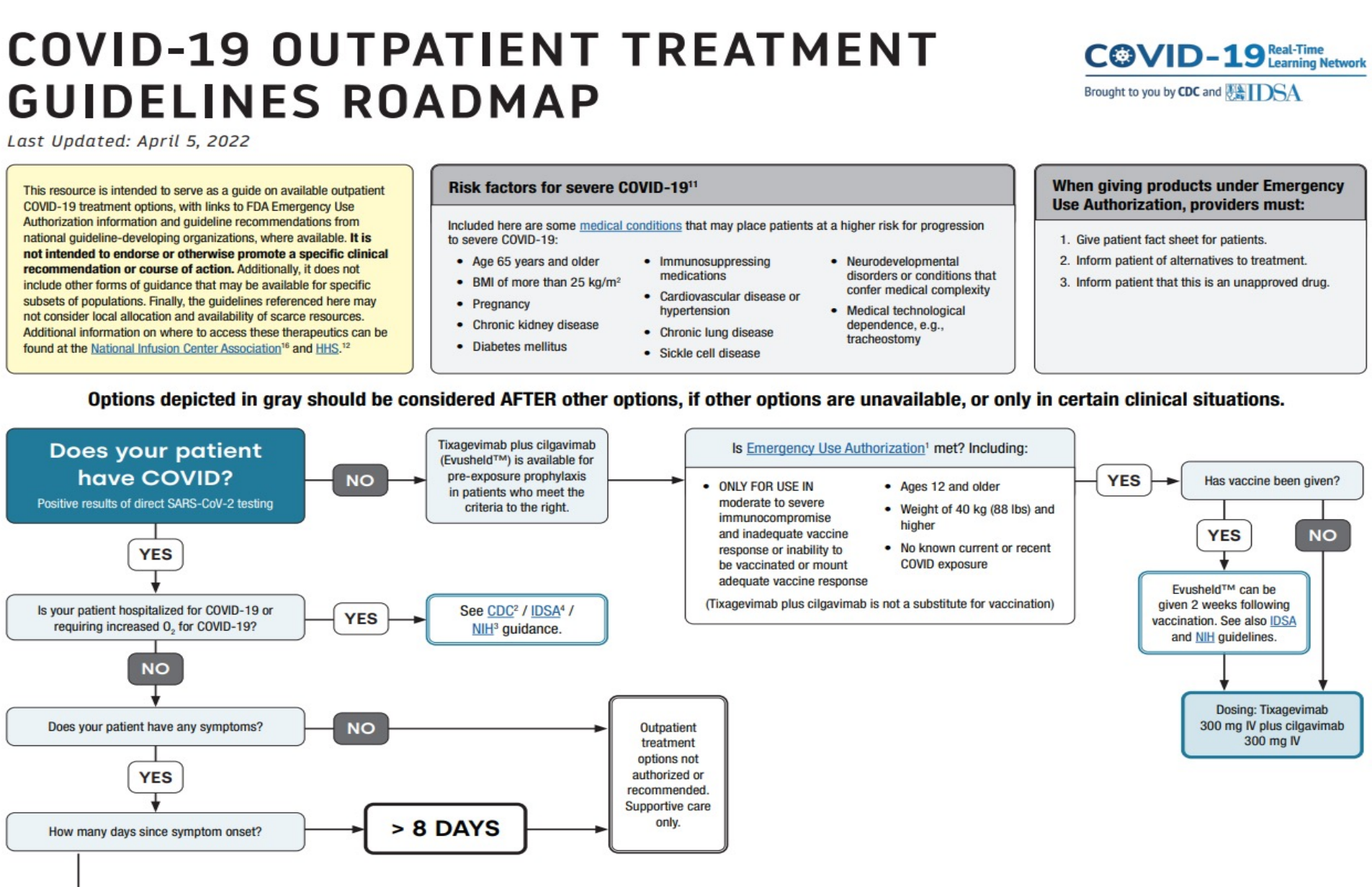
1

2

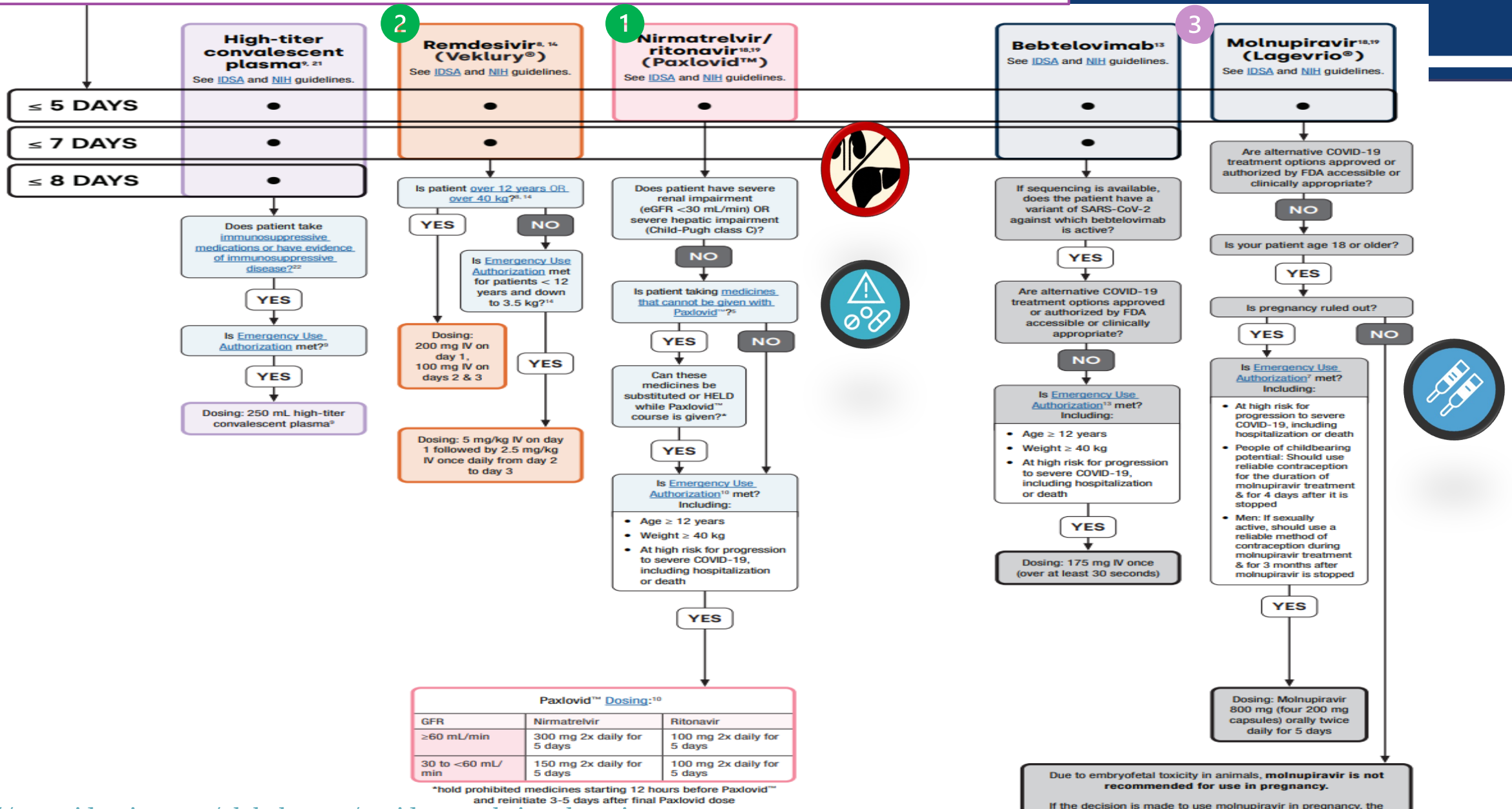
3

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
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

IDSA Outpatient Treatment Roadmap



lab + COVID & symptomatic, not hospitalized, not requiring O2 for COVID



https://www.idsociety.org/globalassets/covid-19-real-time-learning-network/outpatientroadmap-v10.pdf

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

	Drug Name	Dosing Regimen	Time From Symptom Onset[a]
1	**Ritonavir-Boosted Nirmatrelvir (Paxlovid)**	**eGFR ≥60 mL/min:** • Nirmatrelvir 300 mg with RTV 100 mg PO twice daily for 5 days **eGFR ≥30 to <60 mL/min:** • Nirmatrelvir 150 mg with RTV 100 mg PO twice daily for 5 days	≤5 days
	Ritonavir-Boosted Nirmatrelvir (Paxlovid), continued	**eGFR <30 mL/min:** • **Not recommended** **Severe Hepatic Impairment (Child-Pugh Class C):** • **Not recommended**	≤5 days
2	**Remdesivir**	RDV 200 mg IV on Day 1, followed by RDV 100 mg IV once daily on Days 2 and 3.[b,c] Each infusion should be administered over 30–120 minutes. Patients should be observed for ≥1 hour after infusion as clinically appropriate.	≤7 days
3	**Bebtelovimab**	BEB 175 mg as a single IV injection, administered over ≥30 seconds. Patients should be observed for ≥1 hour after injection.	≤7 days
	Molnupiravir	Molnupiravir 800 mg PO twice daily for 5 days	≤5 days

[a] Per EUA criteria or clinical trial entry criteria.

[b] An eGFR <30 mL/min at screening or <90 days before screening was considered an exclusion criterion in the outpatient RDV study PINETREE, but only if a participant's weight was <48 kg. See the Remdesivir section for a discussion of RDV use in patients with renal impairment.

[c] If RDV is administered to patients who have a new or increasing need for supplemental oxygen but who are discharged from the ED because hospital resources are limited and inpatient admission is not possible, the total duration of therapy is ≤5 days.

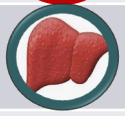
Key: BEB = bebtelovimab; ED = emergency department; eGFR = estimated glomerular filtration rate; EUA = Emergency Use Authorization; IV = intravenous; PO = orally; RDV = remdesivir; RTV = ritonavir

https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf page 59 and 60

Generic Name	1 Nirmatrelvir/ritonavir (Paxlovid) Oral	2 Remdesivir (Veklury) IV	3 Bebtelovimab IV	3 Molnupiravir (Lagevrio) Oral
Manufacturer	Pfizer	Gilead	Eli Lilly and Company	Merck
FDA EUA Date	EUA 12/22/21	4/25/22- No longer on EUA- Fully Authorized for Pediatrics 28 days and older, and at least 3 kg (7lbs)	EUA 3/25/22	EUA 12/23/21
Drug Type/Class/MOA	Antiviral Viral protease inhibitor (Nirmatrelvir) and HIV protease inhibitor & CYP3A inhibitor (ritonavir). Halts viral replication	Antiviral Nucleoside analog (RNA) polymerase inhibitor that halts viral replication	Monoclonal Antibody (mAb) mAb against spike, blocks viral attachment to host cells	Antiviral Nucleoside Analog that inhibits viral replication by viral mutagenesis
Reported efficacy data	88% reduction in hospitalizations/deaths	87% reduction in hospitalizations/deaths	Symptomatic improvement and Day 5 reduction in viral load vs placebo	30% reduction in hospitalization/deaths
Indication	Treatment mild-moderate COVID for at risk patients			
		Treatment of Hospitalized pt with COVID		
Age/weight requirement	12+ (minimum 40 kg or 88 lb)	> 28 days old (min 3.5 kg, 7lb), > 12 years of age (minimum 40 kg, 88lbs)	12+ (minimum 40 kg or 88 lb)	18+ (Adults ONLY)
Rx window	**Within 5 days symptoms onset**	**Within 7 days symptom onset**	**Within 7 days symptom onset**	**Within 5 days symptom onset**
Duration of therapy	**5 days**	**3 days** -not hospitalized, mild-mod COVID-10. **5 days** –hospitalized, not on mech vent/ECMO (extend to **10 days** if not improving) **10 days** -hospitalized, on mech vent/ECMO	**1 Time dose**	**5 days**
Testing Requirements **And lab considerations**	Positive direct SARS-CoV 2 viral test	Positive direct SARS-CoV 2 viral test Baseline renal function required under EUA for pediatric patients As clinically appropriate- perform renal/hepatic lab testing, assess PTT	Positive direct SARS-CoV 2 viral test	Positive direct SARS-CoV 2 viral test
History requirements **Family planning**	Not specified Ritonavir may reduce efficacy of combined hormonal contraceptives. Pt should use effective alternative contraceptive method or additional barrier method of contraception	Not specified	Not specified	**Assess pregnancy status-** not recommended during pregnancy, if childbearing potential, advise of potential risk to fetus, use reliable contraception correctly and consistently for duration of treatment and 4 days after last dose. Males of reproductive potential should use reliable contraception correctly/consistently x 3 months after last dose.

Adapted from https://aspr.hhs.gov/COVID-19/Therapeutics/Documents/side-by-side-overview.pdf

Generic Name	1 Nirmatrelvir/ritonavir (Paxlovid) Oral	2 Remdesivir (Veklury) IV	3 Bebtelovimab IV	3 Molnupiravir (Lagevrio) Oral
Dose	300 mg nirmatrelvir with 100 mg ritonavir Take all 3 tablets PO BID with or without food *(although eating with fatty meal enhances absorption)* **Dosing for Special Population:** **Pediatric patients** 12+ and at least 40 kg: no dosage adjustment **Pregnancy or Lactation:** No dosage adjustment **Renal:** Normal- mild renal impairment eGFR > 60 mL/min: No dosage **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. **Severe renal impairment, eGFR < 30- ml/min- Not recommended** **Hepatic-** Mild/moderate impairment**:** No dosage adjustment **Severe Impairment, Child-Pugh Class – C- Avoid** 	**Adults/Peds 12+ at least 40 Kg:** Single loading dose 200mg Day 1 IV, then maintenance daily dose 100mg IV **Dosing for Special Population:** **Peds > 28 days, and > 3 kg, < 40kg:** Single Loading dose: 5 mg/kg IV Maintenance dose: 2.5 mg/kg IV **Renal:** **Severe renal impairment eGFR < 30: Not recommended** **28+ day old full term neonate with serum creatinine greater than or equal to 1mg/dL- Not recommended** 	175 mg/2ml (87.5 mg/ml) administered via IV injection over 30 seconds **Dosing for Special Population:** **Pediatrics:** If eligible, no dosage adjustment **Pregnancy or Lactation:** No dosage adjustment **Geriatrics:** No dosage adjustment **Renal:** No dosage adjustment **Hepatic:** No dosage adjustment for mild hepatic impairment	800 mg PO q 12 hours (4 capsules per dose) With or without food **Dosing for Special Population:** **Pediatrics:** Not eligible, as it may affect bone and cartilage growth. **Pregnancy or Lactation:** Not recommended for use during pregnancy. Breastfeeding not recommended during treatment or for 4 days after final dose. **Renal:** No dosage adjustment **Hepatic:** No dosage adjustment 
How supplied	5 daily dose blister cards *renal impairment dose packs available	Single Dose Vial 100 mg Remdesivir as lyophilized powder in single dose vial (no reconstituted) 100mg/20ml (5mg/ml) after reconstitution.	Single Dose Vial	Bottle (40 capsules)
Administration details	Ok to take with or without food, but high fat meal increases absorption 15%, pills cannot be crushed	Reconstitute powder by adding 19 ml sterile water. see recommended dilution instructions in package insert. **Monitoring recommended 1 hour after infusion**- for hypersensitivity reaction or infusion reaction 	Administer entire contents via IV injection over at least 30 seconds. See recommended storage/handling instructions in package insert. **Monitoring recommended 1 hour after infusion**- for hypersensitivity reaction or infusion reaction 	Ok to take with or without food, pills cannot be crushed
Adverse Events (if from clinical trials, incidence ≥ 1%)	Dysguesia (altered taste sensation) 6%, diarrhea 3%, hypertension 1%, myalgia 1%	Nausea 10.8%, Headache 5.7%, Cough 3.6%, diarrhea 3.9%, dyspnea 2.5%, fatigue 3.6%, ageusia 2.9%, anosmia 3.2%, dizziness 1.8%, chills 2.2% Lab abnormalities: (10.8%)	Infusion-related: 0.3%, pruritis 0.3%, rash 0.8% Nausea 0.8%, vomiting 0.7%	Diarrhea 2%, nausea 1%, dizziness 1% Lab abnormality: ALT, AST, creatinine, lipase, hemoglobin, platelets, leukocytes- < 2% Post auth experience: Hypersensitivity: anaphylaxis, angioedema Skin disorder: Erythema, rash, urticaria

Generic Name	1 Nirmatrelvir/ritonavir (Paxlovid) Oral	2 Remdesivir (Veklury) IV	3 Bebtelovimab IV	3 Molnupiravir (Lagevrio) Oral
Potential Drug-Drug Interactions	Moderate/High- see prescribing information	Low- See prescribing information	unlikely	None identified
Renal Dose Adjustment	For eGFR 30-60, lower dose advised, not recommended for those with eGFR < 30 ml/min 	Not recommended for those with eGFR < 30 ml/min 	none	None
Hepatic Dose Adjustment	Avoid in severe hepatic impairment (Child-Pugh Class C) 	None- but should monitor LFT before and during treatment 	none	none
Contraindications	Hypersensitivity to ingredients CYP3A4 drug-drug interactions	Hypersensitivity to Veklury or any of its components	none listed	None listed *Not recommended for use in pregnancy- see special populations
Warnings/drug interactions	Beware of drug interactions, hepatoxicity, HIV-1 drug resistance in patients with HIV-1 infection Many drug interactions (statins, blood thinners, OCP, seizure medications, St. John's Wort) should use drug interaction checker tool 	Possible hypersensitivity/infusion related reaction. 	Possible hypersensitivity/infusion related reaction. Clinical worsening after SARs-CoV-2 administration 	Embryo-fetal toxicity, bone and cartilage toxicity- not recommended for patients < 18 because of potential effects on bone/cartilage growth Not recommended for use during pregnancy. No drug interactions identified to date Hypersensitivity reactions 
Special Populations	No human data on use in pregnancy or breastfeeding	Insufficient human data on use during pregnancy or breastfeeding	Insufficient human data on use during pregnancy or breastfeeding	Not recommended in pregnancy. Not recommended if breastfeeding (has pregnancy surveillance program)
cost	$530 per course	$390-520 per dose, or $2,340-3,120 for 5 day tx (hospital)	$ 1,250 per dose	$712 per course

Resources

Generic Name	1 Nirmatrelvir/ritonavir (Paxlovid) Oral	2 Remdesivir (Veklury) IV	3 Bebtelovimab IV	3 Molnupiravir (Lagevrio) Oral
FDA	EUA for treatment of mild-moderate COVID-19 Illness	FDA Approved for COVID-19 Treatment	EUA for treatment of mild-moderate COVID-19 Illness	EUA for treatment of mild-moderate COVID-19 Illness
Activity against Omicron	Other variants: See Section 12.4 of https://www.fda.gov/media/155050/download	Other Variants- see section 15 of https://www.fda.gov/media/137566/download see section 12.4 of https://www.gilead.com/-/media/files/pdfs/medicines/COVID-19/veklury/veklury_pi.pdf	Other variants: See Section 12.4 of https://www.fda.gov/media/156152/download	other variants: See Section 12.4 of https://www.fda.gov/media/155054/download
Product Website	https://www.covid19oralrx.com/	https://www.gilead.com/remdesivir	http://www.lillyantibody.com/bebtelovimab	https://www.molnupiravir-us.com/patients/
FDA Factsheets for HCP	https://www.fda.gov/media/155050/download	https://www.fda.gov/media/137566/download	https://www.fda.gov/media/156152/download	https://www.fda.gov/media/155054/download
FDA Factsheets for patients, parents, caregivers	https://www.fda.gov/media/155051/download	https://www.fda.gov/media/137565/download	https://www.fda.gov/media/156153/download	https://www.fda.gov/media/155055/download

Adapted from ASPR HHS Side by Side Overview of Therapeutics Authorized or Approved for the Prevention of COVID-19 Infection or Treatment of Mild-Moderate COVID-19 : Side-by-Side Overview of Outpatient Therapies Authorized for Treatment of Mild-Moderate COVID-19 (hhs.gov)

Remdesivir study NEJM: https://www.nejm.org/doi/full/10.1056/NEJMoa2116846

Study showing maintained in vitro potency Molnupiravir and Remdesivir against Omicron Variant: https://www.biorxiv.org/content/10.1101/2022.01.17.476685v1

Monoclonal Antibody- Infographic and Toolkit: https://www.cms.gov/files/document/covid-infographic-coverage-monoclonal-antibody-products-treat-covid-19.pdf https://www.cms.gov/monoclonal

https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/covid-19-vaccines-and-monoclonal-antibodies
https://www.hrsa.gov/CovidUninsuredClaim

Paxlovid- Drug Interactions

As a healthcare provider, you should:

- **Inform patients that Paxlovid™ may interact with some drugs and is contraindicated for use with some drugs**
- **Obtain a complete medication list from your patient (including nonprescription drugs and herbals)**
- **Check for clinically significant drug interactions:**
  - Section 7.3 of the EUA Fact Sheet: https://www.fda.gov/media/155050/download
  - NIH Statement on Paxlovid™ Drug-Drug Interactions: https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-paxlovid-drug-druginteractions/
  - https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/management-of-drug-interactions-with-nirmatrelvirritonavir-paxlovid/

- **Based on the drug interactions, decide if:**
  - Paxlovid™ use is appropriate versus an alternative authorized treatment
  - If appropriate, whether your patient should hold, change, or dose-reduce other medications while taking Paxlovid™, or if additional monitoring may be needed

Prescribe an Alternative COVID-19 Therapy

For cases where drug-drug interaction management strategies are not possible or feasible, or the potential risks of such strategies outweigh the potential benefits.

Amiodarone	Flecainide	Propafenone
Apalutamide	Glecaprevir/pibrentasvir	Quinidine
Bosentan	Ivabradine	Rifampin
Carbamazepine	Lumacaftor/ivacaftor	Rifapentine
Clopidogrel[a]	Lumateperone	Sildenafil for PH
Clozapine	Lurasidone	St. John's wort
Disopyramide	Meperidine (pethidine)	Tadalafil for PH
Dofetilide	Midazolam (oral)	Tolvaptan
Dronedarone	Phenobarbital	Vardenafil for PH
Enzalutamide	Phenytoin	Voclosporin
Eplerenone	Pimozide	
Ergot derivatives	Primidone	

Temporarily Withhold Concomitant Medication, If Clinically Appropriate

For guidance on restarting the concomitant medication, consult the Liverpool COVID-19 Drug Interactions website.[b] If withholding is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy.

Alfuzosin	Estazolam[d]	Rosuvastatin
Aliskiren	Everolimus[f]	Salmeterol
Atorvastatin	Finerenone	Silodosin
Avanafil	Flibanserin	Simvastatin
Chemotherapy[c]	Flurazepam[d]	Sirolimus[f]
Clonazepam[d]	Lomitapide	Suvorexant
Clorazepate[d]	Lovastatin	Tacrolimus[f]
Colchicine[e]	Naloxegol	Ticagrelor
Diazepam[d]	Ranolazine	Triazolam[d]
Eletriptan	Rimegepant	Ubrogepant
Erythromycin	Rivaroxaban[g]	Vorapaxar

Adjust Concomitant Medication Dose and Monitor for Adverse Effects

Consult the Liverpool COVID-19 Drug Interactions website[b] for guidance. 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.

Alprazolam[d]	Darifenacin	Pimavanserin
Amlodipine	Digoxin	Quetiapine
Apixaban	Elexacaftor/tezacaftor/ivacaftor	Rifabutin
Aripiprazole	Eluxadoline	Riociguat
Brexpiprazole	Fentanyl	Saxagliptin
Buspirone	Iloperidone	Sildenafil for ED
Cariprazine	Itraconazole	Ruxolitinib
Chlordiazepoxide[d]	Ivacaftor	Tadalafil for ED
Cilostazol	Ketoconazole	Tamsulosin
Clarithromycin	Maraviroc	Tezacaftor/ivacaftor
Clobazam[d]	Mexiletine	Trazodone
Cyclosporine[f]	Oxycodone	Vardenafil for ED

[a] Reduced effectiveness of clopidogrel is likely. Do not coadminister clopidogrel in patients who are at a very high risk of thrombosis (e.g., those who are within 6 weeks of coronary stenting); consider prescribing an alternative antiplatelet (i.e., prasugrel) or an alternative COVID-19 therapy. For other indications, it may be acceptable to continue clopidogrel if the benefit of ritonavir-boosted nirmatrelvir treatment outweighs the risk of reduced clopidogrel effectiveness.

[b] Additional resources include the EUA fact sheet for ritonavir-boosted nirmatrelvir and the FDA prescribing information for the concomitant medication. These may be consulted for medications that are not found on the Liverpool COVID-19 Drug Interactions website.

Do Not Give Paxlovid.

Prescribe/refer to other treatments based on local availability in this order: 1)Remesivir 2)monoclonal antibody tx 3) molnupiravir

Ok to Prescribe Paxlovid

Hold medications on this table while on paxlovid if clinically appropriate. Consult Liverpool website on when to restart concomitant medication(s)

Ok to Prescribe Paxlovid

Consider adjusting dose or if cannot be adjusted, withhold medication listed on this table while patient is on Paxlovid. Consult Liverpool website.

Paxlovid and determining Drug-Drug Interactions

University of Liverpool

Prescribing Resources:

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

Link to pdf

Liverpool Drug Interactions Group

Interactions with Essential Medicines & Nirmatrelvir/ritonavir (NMV/r)

Charts produced 8 March 2022 — Page 1 of 2

Please check www.covid19-druginteractions.org for updates.

Interaction tables - refer to page 2 for legend, notes and abbreviations

Please note that if a drug is not listed it cannot automatically be assumed it is safe to coadminister.
Drug interaction data for many agents are limited or absent; therefore, risk-benefit assessment for any individual patient rests with prescribers.
Management of interactions with nirmatrelvir/ritonavir (Paxlovid) may be complex and full details should be obtained from the website where possible.

Analgesics	
	Codeine
	Diclofenac
☐	Fentanyl
	Hydromorphone
	Ibuprofen
	Mefenamic acid
	Morphine
☐	Oxycodone
	Paracetamol
	Tramadol
Antiarrhythmics	
!	Amiodarone
☐	Lidocaine
Antibacterials	
	Amikacin
	Amoxicillin
	Ampicillin
☐	Bedaquiline
	Cefalexin
	Cefazolin
	Cefixime
	Cefotaxime
	Ceftriaxone
	Chloramphenicol
	Ciprofloxacin
	Clarithromycin (a)
	Clindamycin
	Clofazimine
	Cloxacillin
	Cycloserine
	Dapsone
☐	Delamanid
	Doxycycline
☐	Erythromycin
	Ethambutol
	Ethionamide
	Gentamicin
	Imipenem/cilastatin
	Isoniazid
	Kanamycin
	Levofloxacin
	Linezolid
	Meropenem
	Metronidazole
	Moxifloxacin
	Nitrofurantoin
	Ofloxacin
	Para-aminosalicylic acid
	Penicillins
	Piperacillin
	Pyrazinamide
☐	Rifabutin (b)
✖	Rifampicin
✖	Rifapentine
	Spectinomycin
	Streptomycin
	Sulfadiazine
	Tazobactam
	Tetracyclines
	Trimethoprim/ sulfamethoxazole
	Vancomycin

Anticoagulants/antiplatelets	
	Apixaban
	Aspirin (antiplatelet)
	Clopidogrel (stented) (c)
	Dabigatran (a)
	Dalteparin
	Edoxaban (d)
	Enoxaparin
	Heparin
	Rivaroxaban
	Streptokinase
☐	Warfarin
Anticonvulsants	
✖	Carbamazepine
	Clonazepam
☐	Ethosuximide
	Lamotrigine
✖	Phenobarbital
✖	Phenytoin
	Valproate
Antidepressants	
	Amitriptyline
	Clomipramine
	Fluoxetine
	Lithium
Antidiabetics	
	Glibenclamide
	Gliclazide
	Insulin
	Metformin
Antifungals	
	Amphotericin B
	Fluconazole
	Flucytosine
	Griseofulvin
	Itraconazole (e)
	Ketoconazole (e)
	Nystatin
☐	Voriconazole
Antimalarials	
☐	Amodiaquine
	Artemether
	Artesunate
	Atovaquone
	Lumefantrine
☐	Mefloquine
☐	Piperaquine
	Primaquine
	Proguanil
☐	Quinine
Antipsychotics	
	Chlorpromazine
	Clozapine
	Fluphenazine
☐	Haloperidol
☐	Risperidone
Anxiolytics	
	Diazepam
	Lorazepam
	Midazolam

Beta blockers	
	Atenolol
	Bisoprolol
	Carvedilol
	Metoprolol
	Propranolol
	Timolol
Bronchodilators	
	Aminophylline
	Ipratropium bromide
	Salmeterol
Calcium channel blockers	
	Amlodipine
	Nifedipine
	Verapamil
Cancer drugs	
☐	Dasatinib (f)
☐	Erlotinib (g)
☐	Imatinib (h)
	Methotrexate
☐	Vinblastine (i)
Contraceptives	
	Ethinylestradiol
	Etonogestrel (IMP)
	Etonogestrel (VR)
	Levonorgestrel (COC)
	Levonorgestrel (EC)
	Levonorgestrel (IDU)
	Levonorgestrel (POP)
	Medroxyprogesterone (depot injection)
	Norethisterone (COC)
	Norethisterone (IM)
	Norethisterone (POP)
	Norgestrel (COC)
COVID19 therapies	
	Budesonide (inhaled)
	Convalescent plasma
	Dexamethasone
	Hydrocortisone
	Infliximab
	Methylprednisolone
	COVID19 vaccines
Gastrointestinal agents	
☐	Aprepitant
	Domperidone
	Lactulose
	Loperamide
	Mesalazine
	Metoclopramide
	Omeprazole
	Ondansetron
	Ranitidine
	Senna
HCV antivirals	
	Glecaprevir/pibrentasvir
	Ledipasvir/sofosbuvir
	Ombitasvir/paritaprevir/r
	Sofosbuvir/velpatasvir
Herbals/supplements	
	Folic acid
	Magnesium
	St John's Wort

HIV antiretrovirals	
	Abacavir
	Atazanavir/ritonavir
	Darunavir/ritonavir
	Dolutegravir
	Efavirenz
	Emtricitabine
	Lamivudine
	Lopinavir/ritonavir
	Nevirapine
	Raltegravir
	Tenofovir alafenamide
	Tenofovir-DF
	Zidovudine
Hypertension/heart failure	
	Amiloride
☐	Digoxin
	Dopamine
	Enalapril
	Furosemide
	Hydrochlorothiazide
	Isosorbide dinitrate
	Lisinopril
	Losartan
	Methyldopa
	Spironolactone
Immunosuppressants	
	Azathioprine
	Ciclosporin
	Everolimus
Lipid lowering agents	
☐	Atorvastatin
	Fluvastatin
	Lovastatin
	Simvastatin
Others	
	Allopurinol
	Ergometrine
	Levodopa
	Levothyroxine
Steroids	
	Beclomethasone
	Betamethasone
	Fludrocortisone
	Prednisolone
	Testosterone
☐	Triamcinolone

Link to pdf

Liverpool Drug Interactions Group

Assessing a patient for Paxlovid (nirmatrelvir/ritonavir)

Updated 10 March 2022 — Page 1 of 1

Please check www.covid19-druginteractions.org for updates.
Data are limited or absent; therefore, risk-benefit assessment for any individual patient rests with prescribers.
Developed by Kirsteen Hill, ID/HIV/COVID Pharmacist, Dundee, Scotland and adopted by Liverpool Drug Interactions Group.

ANY OF THE FOLLOWING:
- **<18 years** (check local age restrictions)
- **Pregnancy** (discuss the benefits/risks of treatment with the patient and a multidisciplinary team)
- **Severe renal impairment:** eGFR (CrCl if >75years) <30 ml/min
- **Severe liver disease:** Child Pugh Class C
- **Unable to swallow tablets**
- **Prescribed any medicines below:**

Amiodarone	Pethidine
Alfuzosin*	Phenobarbitone
Aliskiren	Primidone
Apixaban*	Pimozide
Bosentan	Phenytoin
Carbamazepine	Quetiapine
Ciclosporin	Ranolazine
Clozapine	Rifampicin
Clonazepam	Rivaroxaban*
Colchicine	Salmeterol*
Diazepam*	Sildenafil *(pulmonary hypertension)*
Disopyramide	Simvastatin*
Domperidone*	Sirolimus
Dronedarone	St John's Wort
Enzalutamide	Tacrolimus
Eplerenone	Tadalafil *(pulmonary hypertension)*
Flecainide	Ticagrelor
Ivabradine	
Lercanidipine*	
Midazolam (oral)	

**unless medicine can be stopped safely for 8 days*

Note: list of medicines not exhaustive and subject to change

YES → **No Paxlovid**

NO

Use covid19-druginteractions.org **(or Paxlovid product label if medicine not listed) to check all medicines** including:**
- OTC medicines
- Recreational drugs
- Prescription medicines e.g.,
  - systemic anticancer treatment (SACT) within last 28 days
  - opiate substitution therapy
  - HCV/HBV/HIV treatment
  - steroid injections
  - depot antipsychotics
  - multiple sclerosis treatment

** *No need to check medicines below on interaction website (list not exhaustive):*
ACE inhibitors
Acid reducing agents (antacids, PPIs, H2RAs)
Aspirin
Azathioprine
Beta Blockers
Contraceptives/HRT
Corticosteroids (oral/inhaled/topical)
Fluvastatin
Furosemide
Gabapentin
Immunoglobulin
Inhalers (except salmeterol)
Insulin
Levothyroxine
Metformin
Methotrexate
Monoclonal antibodies (MABs)
Mycophenolate
NSAIDs (except piroxicam)
Pravastatin
Pregabalin

ANY RED/AMBER INTERACTIONS?

YES → Review full information on covid19-druginteractions.org **and consider practicalities of advice/monitoring:**
- Can medicine be withheld safely for 8 days? e.g., simvastatin
- Can a dose adjustment be done easily? e.g., be aware of patients on compliance devices or those who do not have tablets/liquid to allow dose change, or if there is concern re patient understanding. Consider alternative day dosing if a dose change is impractical.
- Can the patient be advised regarding which adverse reactions to be aware of and what to do?

Clinical decision (including consulting a specialist if appropriate) based on all the individual patient information and discussion with patient to prescribe Paxlovid.

NO → **No Paxlovid**

NO

eGFR (CrCl if >75 years) ≥60 ml/min

YES → ✓ **Paxlovid Full Dose** — Nirmatrelvir 300 mg (2 x 150 mg) twice daily + Ritonavir 100 mg (1 tablet) twice daily for 5 days

NO → ✓ **Paxlovid ↓ Dose** — Nirmatrelvir 150 mg (1 x 150 mg) twice daily + Ritonavir 100 mg (1 tablet) twice daily for 5 days

Link to pdf

Liverpool Drug Interactions Group

Interactions with Essential Medicines & Nirmatrelvir/ritonavir (NMV/r)

Charts produced 8 March 2022 — Page 2 of 2

Please check www.covid19-druginteractions.org for updates.

Legend

Colour/Symbol		Recommendation for NMV/r use
!	**Do not co-administer**	**Do not use NMV/r ⇒ alternative COVID-19 therapy** Risk of serious toxicity. Stopping the drug does not mitigate the interaction due to its prolonged half-life.
✖	**Do not co-administer**	**Do not use NMV/r ⇒ alternative COVID-19 therapy** Strong inducer can jeopardize NMV/r efficacy due to persisting induction after stopping the drug.
	Do not co-administer	NMV/r use ONLY possible if drug is paused or replaced by a non-interacting drug Risk of serious toxicity. Only start NMV/r if the drug can be safely paused or replaced. Drug can be resumed 3 days after completing NMV/r therapy.
☐	**Potential interaction** Dose adjustment and/or close monitoring required.	Stop or replace drug if possible or consult specialist for dose adjustment/monitoring to allow use with NMV/r Ideally, only start NMV/r if the drug can be safely paused or replaced. Alternatively, dose adjust/monitor. Refer to www.covid19-druginteractions.org for detailed information.
	Potential interaction Manageable by counselling patient	Proceed with NMV/r Interaction manageable by counselling the patient about potential interaction and advising to temporarily stop the drug if feeling unwell.
	Weak interaction No action needed	Proceed with NMV/r Drug metabolized partially by CYP3A4 or with low risk of adverse event from interaction.
	No interaction expected	Proceed with NMV/r

Paxlovid™ Summary

- Paxlovid™ was authorized on 12/22/21 for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older and ≥40 kg) who are at high risk for progression to severe COVID-19*.
- Paxlovid™ reduced COVID-19 related hospitalization and death by 88% when given within 5 days of symptom onset, without concerning safety findings, in the clinical trial EPIC-HR.
- Key Things to Remember When Prescribing:
  - Multiple drug interactions
  - Reduced dose for moderate renal impairment
  - Not recommended with severe renal impairment or severe hepatic impairment

*Paxlovid™ may be used regardless of COVID-19 vaccination status under EUA

What about COVID-19 Rebound after Paxlovid Treatment

CDC Health Advisory May 24, 2022

https://emergency.cdc.gov/han/2022/han00467.asp

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.

Recommendations for Healthcare Providers

For patients with COVID-19 rebound

- There is currently no evidence that additional treatment for COVID-19 is needed for COVID-19 rebound. Based on data available at this time, patient monitoring continues to be the most appropriate management for patients with recurrence of symptoms after completion of a treatment course of Paxlovid.
- Advise people with COVID-19 rebound to follow CDC's guidance on isolation and take precautions to prevent further transmission. Patients should re-isolate for at least 5 days. Per CDC guidance, they can end their re-isolation period after 5 full days if fever has resolved for 24 hours (without the use of fever-reducing medication) and symptoms are improving. The patient should wear a mask for a total of 10 days after rebound symptoms started.
- Consider clinical evaluation of patients who have COVID-19 rebound and symptoms that persist or worsen.
- Healthcare providers are encouraged to report cases of COVID-19 rebound to Pfizer after Paxlovid treatment using the following online tool: Pfizer Safety Reportingexternal icon and to FDA MedWatch. Complete and submit a MedWatch formexternal icon, or complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178). Call 1-800-FDA-1088 for questions.

3) Alternative Therapeutic- Molnupiravir

- **MOV is not recommended for use during pregnancy**
  - Based on animal data, MOV may cause fetal harm when administered to pregnant individuals

- However, if a healthcare provider determines that the benefits outweigh the risks for an individual pregnant patient, they must:
  - Counsel the patient regarding the known and potential benefits and potential risks of MOV use during pregnancy
  - Document that the patient is aware of the known and potential benefits and potential risks of MOV 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 https://pregnancyreporting.msd.com

3) Molnupiravir- Prescriber Requirements

- Provide an electronic or hard copy of patient fact sheet and document that patient has received an electronic or hard copy of the patient fact sheet
- Review the information contained within the patient factsheet with the patient and counsel patient on the known and potential benefits and risks of MOV
- Assess whether an individual of childbearing potential is pregnant or not, if clinically indicated
- Advise individuals of childbearing potential to use contraception for the duration of treatment and for 4 days after the last dose of MOV
- Advise sexually active individuals with partners of childbearing potential to use contraception during treatment and for at least 3 months after the last dose of MOV
- Make individuals of childbearing potential aware of pregnancy surveillance program
- Report all medication errors and serious adverse events potentially related to MOV within 7 calendar days from the healthcare provider's awareness of the event
  - www.fda.gov/medwatch/report.htm
  - or call 1-800-FDA-1088
- See prior slide for requirements for use in pregnancy

Therapeutic Algorithm for Covid-19 Patient with Mild-Moderate Symptoms

At high-risk for progression to severe disease if COVID-19 positive?

** This is regardless of vaccination status.

NO → STOP

Yes ↓

Within 5 Days of Symptoms Onset?

NO → If within 7 days of symptoms onset, refer for monoclonal antibody treatment.

Yes ↓

eGFR > 30 and not in Child-Pugh C

NO → Can consider Molnupiravir after careful review of safety profile in EUA. **Contraindicated in pregnant women**

Yes ↓

dated 4/15/22

Mild-moderate symptoms = does **not** require hospitalization or supplemental oxygen

Medical Conditions at High-Risk for Progression to Severe Disease if COVID-19 Positive

- Cancer
- Chronic Kidney Disease
- Tuberculosis
- Chronic Liver Disease
- Chronic Lung Disease
- Substance use Disorders
- Cystic Fibrosis
- Dementia or other Neurological Conditions
- Stroke or Cerebrovascular Disease
- Diabetes (Type 1 or 2)
- Disabilities
- Solid or Blood Stem Cell Transplant
- Heart Conditions
- HIV Infection
- Smoking, Current or Former
- Immunocompromised State (Weakened Immune System)
- Mental Health Conditions
- Sickle Cell Disease or Thalassemia
- Overweight And Obesity
- Pregnancy

Source: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

Also, anyone age 65 years and older, regardless of vaccination status, should be considered.

Current supply of COVID-19 Outpatient therapeutics

- Supply of therapeutics in California is currently NOT limited!
- Doses are more readily available across the county
- All patients who are eligible for treatment with COVID-19 treatments should be offered treatment to reduce potential for hospitalization
- If therapeutics become scarce, clinicians should use NIH treatment guidelines to prioritize higher risk individuals

Where to find doses

- HHS Therapeutic Locator: https://covid-19-therapeutics-locator-dhhs.hub.arcgis.com
- HHS Test to Treat: https://covid-19-test-to-treat-locator-dhhs.hub.arcgis.com

Test to Treat

- Federal initiative launched in March to provide quick access to free treatment for COVID-19
- One-Stop Test to Treat sites where people are able to get tested and if they are positive and treatments are appropriate, can also receive a prescription from a health care provider (either on site or through telehealth) and have their prescription filled all at one location
- “One-Stop Test to Treat” sites are available at thousands of locations nationwide, including pharmacy-based clinics, federally-funded health centers, long-term care facilities, and community-based sites.
- In May, the program was expanded to include federally-supported Test to Treat sites.

https://aspr.hhs.gov/TestToTreat/Pages/default.aspx

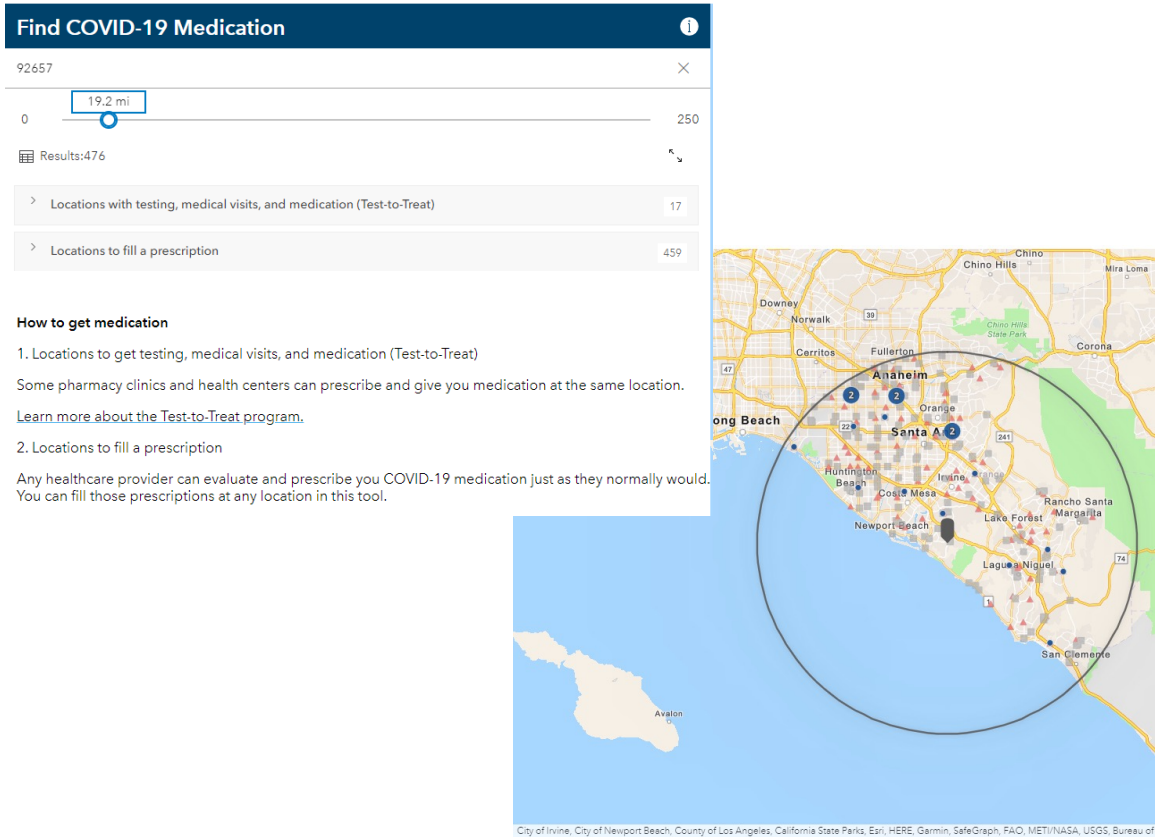
Note, even if a “Test to Treat” site is not available in a given location

- Health care providers throughout the county who can appropriately assess individuals and have prescribing abilities can prescribe the oral viral therapeutics to pharmacy sites that carry the oral antivirals.

https://aspr.hhs.gov/TestToTreat/Documents/Fact-Sheet.pdf

Finding Therapeutics

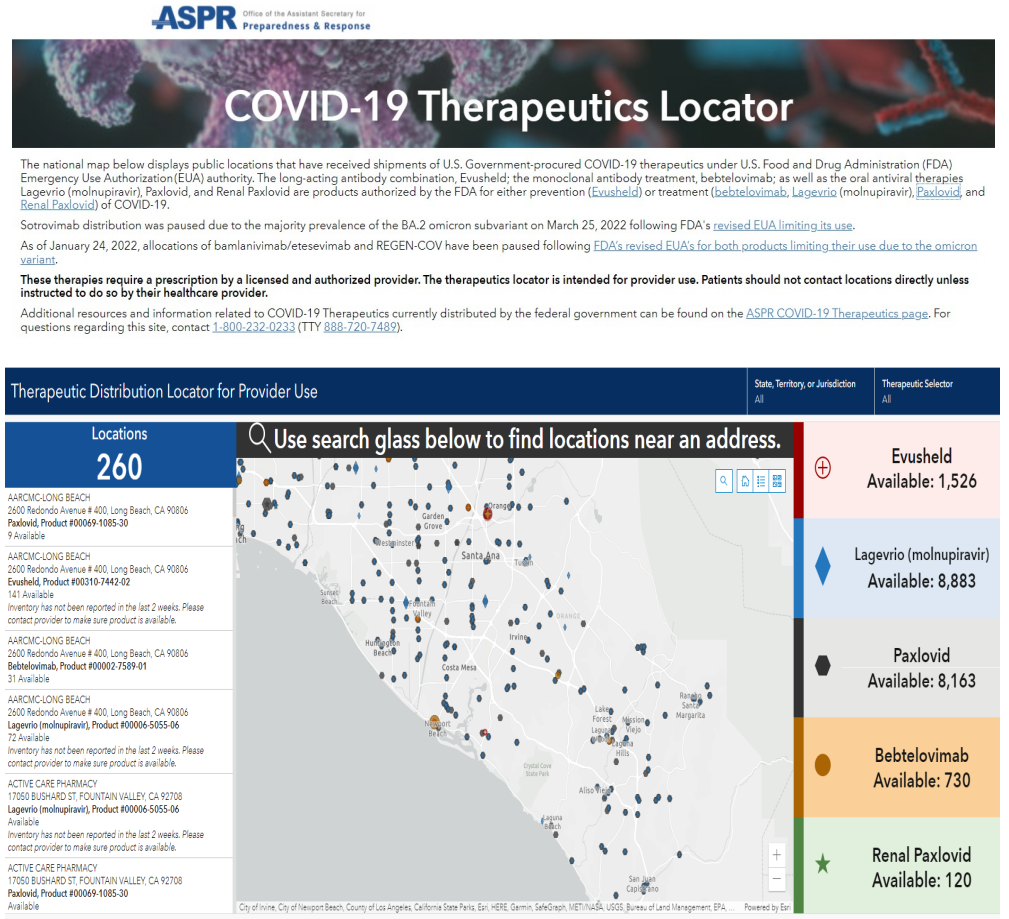
Test to Treat locator for Patients



Need help finding a place to get medication? Call 1-800-232-0233 (TTY 888-720-7489)

https://covid-19-test-to-treat-locator-dhhs.hub.arcgis.com/

COVID-19 Therapeutics Locator for Clinicians



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

Case Discussions

Case 1:
66 y/o M
Sx: 3 days fever/cough + home antigen test
PMH: no renal/hepatic impairment
Meds: none

What if the case was
45 y/o? M Vs F
Ethnicity: non-White
unsheltered?

Medical Conditions at High-Risk for Progression to Severe Disease if COVID-19 Positive

- Cancer
- Chronic Kidney Disease
- Tuberculosis
- Chronic Liver Disease
- Chronic Lung Disease
- Substance use Disorders
- Cystic Fibrosis
- Dementia or other Neurological Conditions
- Stroke or Cerebrovascular Disease
- Diabetes (Type 1 or 2)
- Disabilities
- Solid or Blood Stem Cell Transplant
- Heart Conditions
- HIV Infection
- Smoking, Current or Former
- Immunocompromised State (Weakened Immune System)
- Mental Health Conditions
- Sickle Cell Disease or Thalassemia
- Overweight And Obesity
- Pregnancy

Source: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

Also, anyone age 65 years and older, regardless of vaccination status, should be considered.

Paxlovid Candidate?

1) Verify SARS-CoV-2 infection (antigen/PCR), mild-moderate illness
2) Verify < 5 days from symptom onset
3) Is the patient at high risk for developing severe illness?
4) Age/weight appropriate for paxlovid?
5) Cautions
    1) eGFR > 30? eGFR 31-60? > 60
    2) No severe hepatic impairment (Child-Pugh C)?
6) Med Interactions? Can meds be adjusted?

1) Yes
2) Yes
3) High risk- age
4) Meets age requirement
5) No renal/hepatic impairment
6) No med interactions

Good Paxlovid Candidate!
Prescribe regular Paxlovid pack!

Can consider at high risk with ethnicity/unsheltered status!

Case Discussions

Case 2:

48 y/o F, fully vaccinated and boosted

Sx: 3 days sore throat, headache, + home antigen test

PMH: BMI 25, HTN, DM, HLP
Moderate renal impairment eGRF 45

Meds: amlodipine, saxagliptin, simvastatin

Case 3:

45 y/o F, fully vaccinated and boosted
Pregnant

Sx: 3 days sore throat, headache, + home antigen test

PMH: BMI 25, HTN, DM, HLP
Moderate renal impairment eGRF 45

Meds: Hydralazine, regular insulin

Paxlovid Candidate?

1) Verify SARS-CoV-2 infection (antigen/PCR), mild-moderate illness
2) Verify < 5 days from symptom onset
3) Is the patient at high risk for developing severe illness?
4) Age/weight appropriate for paxlovid?
5) Cautions
   1) eGFR > 30? eGFR 31-60? > 60
   2) No severe hepatic impairment (Child-Pugh C)?
6) Med Interactions? Can meds be adjusted?

1) Yes
2) Yes
3) High risk- PMH
4) Meets age requirement
5) + moderate renal impairement
6) + med interactions- can be adjusted

Consider
1) Paxlovid- renally dosed, adjust HTN/DM meds, temporarily hold Simvastatin
Or
2) Remdesivir
Case 2- If 1 and 2 not available, then mAb or MOV
Case 3- consider mAB if 1 and 2 not available

Prescribe an Alternative COVID-19 Therapy

For cases where drug-drug interaction management strategies are not possible or feasible, or the potential risks of such strategies outweigh the potential benefits.

Amiodarone	Flecainide	Propafenone
Apalutamide	Glecaprevir/pibrentasvir	Quinidine
Bosentan	Ivabradine	Rifampin
Carbamazepine	Lumacaftor/ivacaftor	Rifapentine
Clopidogrel[a]	Lumateperone	Sildenafil for PH
Clozapine	Lurasidone	St. John's wort
Disopyramide	Meperidine (pethidine)	Tadalafil for PH
Dofetilide	Midazolam (oral)	Tolvaptan
Dronedarone	Phenobarbital	Vardenafil for PH
Enzalutamide	Phenytoin	Voclosporin
Eplerenone	Pimozide	
Ergot derivatives	Primidone	

Temporarily Withhold Concomitant Medication, If Clinically Appropriate

For guidance on restarting the concomitant medication, consult the Liverpool COVID-19 Drug Interactions website.[b] If withholding is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy.

Alfuzosin	Estazolam[d]	Rosuvastatin
Aliskiren	Everolimus[f]	Salmeterol
Atorvastatin	Finerenone	Silodosin
Avanafil	Flibanserin	Simvastatin
Chemotherapy[c]	Flurazepam[d]	Sirolimus[f]
Clonazepam[d]	Lomitapide	Suvorexant
Clorazepate[d]	Lovastatin	Tacrolimus[f]
Colchicine[e]	Naloxegol	Ticagrelor
Diazepam[d]	Ranolazine	Triazolam[d]
Eletriptan	Rimegepant	Ubrogepant
Erythromycin	Rivaroxaban[g]	Vorapaxar

Adjust Concomitant Medication Dose and Monitor for Adverse Effects

Consult the Liverpool COVID-19 Drug Interactions website[b] for guidance. 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.

Alprazolam[d]	Darifenacin	Pimavanserin
Amlodipine	Digoxin	Quetiapine
Apixaban	Elexacaftor/tezacaftor/ivacaftor	Rifabutin
Aripiprazole	Eluxadoline	Riociguat
Brexpiprazole	Fentanyl	Saxagliptin
Buspirone	Iloperidone	Sildenafil for ED
Cariprazine	Itraconazole	Ruxolitinib
Chlordiazepoxide[d]	Ivacaftor	Tadalafil for ED
Cilostazol	Ketoconazole	Tamsulosin
Clarithromycin	Maraviroc	Tezacaftor/ivacaftor
Clobazam[d]	Mexiletine	Trazodone
Cyclosporine[f]	Oxycodone	Vardenafil for ED

[a] Reduced effectiveness of clopidogrel is likely. Do not coadminister clopidogrel in patients who are at a very high risk of thrombosis (e.g., those who are within 6 weeks of coronary stenting); consider prescribing an alternative antiplatelet (i.e., prasugrel) or an alternative COVID-19 therapy. For other indications, it may be acceptable to continue clopidogrel if the benefit of ritonavir-boosted nirmatrelvir treatment outweighs the risk of reduced clopidogrel effectiveness.

[b] Additional resources include the EUA fact sheet for ritonavir-boosted nirmatrelvir and the FDA prescribing information for the concomitant medication. These may be consulted for medications that are not found on the Liverpool COVID-19 Drug Interactions website.

Case Discussions

Case 3:
35 y/o F, fully vaccinated and boosted
Sx: 3 days sore throat, headache, + home antigen test
PMH: BMI 25, HTN, DM, HLP
eGFR < 30
Meds: Metformin, Simvastatin, Amlodipine, OCP

Paxlovid Candidate?

1) Verify SARS-CoV-2 infection (antigen/PCR), mild-moderate illness
2) Verify < 5 days from symptom onset
3) Is the patient at high risk for developing severe illness?
4) Age/weight appropriate for paxlovid?
5) Cautions
    1) eGFR > 30? eGFR 31-60? > 60
    2) No severe hepatic impairment (Child-Pugh C)?
6) Med Interactions? Can meds be adjusted?

**Medical Conditions at High-Risk for Progression to Severe Disease if COVID-19 Positive

- Cancer
- Chronic Kidney Disease
- Tuberculosis
- Chronic Liver Disease
- Chronic Lung Disease
- Substance use Disorders
- Cystic Fibrosis
- Dementia or other Neurological Conditions
- Stroke or Cerebrovascular Disease
- Diabetes (Type 1 or 2)
- Disabilities
- Solid or Blood Stem Cell Transplant
- Heart Conditions
- HIV Infection
- Smoking, Current or Former
- Immunocompromised State (Weakened Immune System)
- Mental Health Conditions
- Sickle Cell Disease or Thalassemia
- Overweight And Obesity
- Pregnancy

Source: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

Also, anyone age 65 years and older, regardless of vaccination status, should be considered.

1) Yes
2) Yes
3) High risk- PMH
4) Meets age requirement
5) + renal/hepatic impairment
6) + med interactions

Not a good candidate for paxlovid or Remdesivir- eGFR < 30

Consider
Bebtelovimab
If not available,
Consider Molnupiravir
continue OCP! Inform about embryo-fetal toxicity risk

Prescribe an Alternative COVID-19 Therapy

For cases where drug-drug interaction management strategies are not possible or feasible, or the potential risks of such strategies outweigh the potential benefits.

Amiodarone	Flecainide	Propafenone
Apalutamide	Glecaprevir/pibrentasvir	Quinidine
Bosentan	Ivabradine	Rifampin
Carbamazepine	Lumacaftor/ivacaftor	Rifapentine
Clopidogrel[a]	Lumateperone	Sildenafil for PH
Clozapine	Lurasidone	St. John's wort
Disopyramide	Meperidine (pethidine)	Tadalafil for PH
Dofetilide	Midazolam (oral)	Tolvaptan
Dronedarone	Phenobarbital	Vardenafil for PH
Enzalutamide	Phenytoin	Voclosporin
Eplerenone	Pimozide	
Ergot derivatives	Primidone	

Temporarily Withhold Concomitant Medication, If Clinically Appropriate

For guidance on restarting the concomitant medication, consult the Liverpool COVID-19 Drug Interactions website.[b] If withholding is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy.

Alfuzosin	Estazolam[d]	Rosuvastatin
Aliskiren	Everolimus[f]	Salmeterol
Atorvastatin	Finerenone	Silodosin
Avanafil	Flibanserin	Simvastatin
Chemotherapy[c]	Flurazepam[d]	Sirolimus[f]
Clonazepam[d]	Lomitapide	Suvorexant
Clorazepate[d]	Lovastatin	Tacrolimus[f]
Colchicine[e]	Naloxegol	Ticagrelor
Diazepam[d]	Ranolazine	Triazolam[d]
Eletriptan	Rimegepant	Ubrogepant
Erythromycin	Rivaroxaban[g]	Vorapaxar

Adjust Concomitant Medication Dose and Monitor for Adverse Effects

Consult the Liverpool COVID-19 Drug Interactions website[b] for guidance. 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.

Alprazolam[d]	Darifenacin	Pimavanserin
Amlodipine	Digoxin	Quetiapine
Apixaban	Elexacaftor/tezacaftor/ivacaftor	Rifabutin
Aripiprazole	Eluxadoline	Riociguat
Brexpiprazole	Fentanyl	Saxagliptin
Buspirone	Iloperidone	Sildenafil for ED
Cariprazine	Itraconazole	Ruxolitinib
Chlordiazepoxide[d]	Ivacaftor	Tadalafil for ED
Cilostazol	Ketoconazole	Tamsulosin
Clarithromycin	Maraviroc	Tezacaftor/ivacaftor
Clobazam[d]	Mexiletine	Trazodone
Cyclosporine[f]	Oxycodone	Vardenafil for ED

[a] Reduced effectiveness of clopidogrel is likely. Do not coadminister clopidogrel in patients who are at a very high risk of thrombosis (e.g., those who are within 6 weeks of coronary stenting); consider prescribing an alternative antiplatelet (i.e., prasugrel) or an alternative COVID-19 therapy. For other indications, it may be acceptable to continue clopidogrel if the benefit of ritonavir-boosted nirmatrelvir treatment outweighs the risk of reduced clopidogrel effectiveness.

[b] Additional resources include the EUA fact sheet for ritonavir-boosted nirmatrelvir and the FDA prescribing information for the concomitant medication. These may be consulted for medications that are not found on the Liverpool COVID-19 Drug Interactions website.

Case Discussion- Peds

Case 4:

12 y/o M, 95 lbs
Sx: 3 days fever/cough + home antigen test
PMH: ADHD, moderate-severe asthma, sickle cell disease, obese
Meds:
- **Albuterol inhaler**
- **Adderall**
- **prednisone**

Case 5:

6 month old

Fever, appears hydrated

+ COVID-19 molecular test

PMH: Congenital heart disease

Case 4: Paxlovid candidate
Or Remdesivir

Case 5: Remdesivir Candidate (ped dose)

Medical Conditions at High-Risk for Progression to Severe Disease if COVID-19 Positive

- Cancer
- Chronic Kidney Disease
- Tuberculosis
- Chronic Liver Disease
- Chronic Lung Disease
- Substance use Disorders
- Cystic Fibrosis
- Dementia or other Neurological Conditions
- Stroke or Cerebrovascular Disease
- Diabetes (Type 1 or 2)
- Disabilities
- Solid or Blood Stem Cell Transplant
- Heart Conditions
- HIV Infection
- Smoking, Current or Former
- Immunocompromised State (Weakened Immune System)
- Mental Health Conditions
- Sickle Cell Disease or Thalassemia
- Overweight And Obesity
- Pregnancy

Source: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

Also, anyone age 65 years and older, regardless of vaccination status, should be considered.

Paxlovid Candidate?

1) Verify SARS-CoV-2 infection (antigen/PCR), mild-moderate illness
2) Verify < 5 days from symptom onset
3) Is the patient at high risk for developing severe illness?
4) Age/weight appropriate for paxlovid?
5) Cautions
   1) eGFR > 30? eGFR 31-60? > 60
   2) No severe hepatic impairment (Child-Pugh C)?
6) Med Interactions? Can meds be adjusted?

Remdesivir Candidate?

Prescribe an Alternative COVID-19 Therapy

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Eplerenone	Pimozide	
Ergot derivatives	Primidone	

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Colchicine[e]	Naloxegol	Ticagrelor
Diazepam[d]	Ranolazine	Triazolam[d]
Eletriptan	Rimegepant	Ubrogepant
Erythromycin	Rivaroxaban[g]	Vorapaxar

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Brexpiprazole	Fentanyl	Saxagliptin
Buspirone	Iloperidone	Sildenafil for ED
Cariprazine	Itraconazole	Ruxolitinib
Chlordiazepoxide[d]	Ivacaftor	Tadalafil for ED
Cilostazol	Ketoconazole	Tamsulosin
Clarithromycin	Maraviroc	Tezacaftor/ivacaftor
Clobazam[d]	Mexiletine	Trazodone
Cyclosporine[f]	Oxycodone	Vardenafil for ED

[a] Reduced effectiveness of clopidogrel is likely. Do not coadminister clopidogrel in patients who are at a very high risk of thrombosis (e.g., those who are within 6 weeks of coronary stenting); consider prescribing an alternative antiplatelet (i.e., prasugrel) or an alternative COVID-19 therapy. For other indications, it may be acceptable to continue clopidogrel if the benefit of ritonavir-boosted nirmatrelvir treatment outweighs the risk of reduced clopidogrel effectiveness.

[b] Additional resources include the EUA fact sheet for ritonavir-boosted nirmatrelvir and the FDA prescribing information for the concomitant medication. These may be consulted for medications that are not found on the Liverpool COVID-19 Drug Interactions website.

Question and Answer

Resources

Treatment

- NIH Guidance: https://www.covid19treatmentguidelines.nih.gov
- COVID-19 Drug Interaction Tool: https://covid19-druginteractions.org/checker
- CDPH Webpage: https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/COVID-19/Treatments.aspx
- HHS: https://www.phe.gov/emergency/events/COVID19/therapeutics/Pages/healthcare-professionals.aspx
- CDC: **https://www.cdc.gov/coronavirus/2019-ncov/your-health/treatments-for-severe-illness.html**
- IDSA: **https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/**

Locating Therapeutic Options

- HHS Therapeutic Locator: https://covid-19-therapeutics-locator-dhhs.hub.arcgis.com
- HHS Test to Treat: https://covid-19-test-to-treat-locator-dhhs.hub.arcgis.com

Fact Sheets for Providers

- FDA EUA: **https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#covid19euas**
- Paxlovid: https://www.fda.gov/media/155050/download
- Remdesivir:
  - Use in ≥ 12 years of age: https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf
  - Use in <12 years of age: https://www.fda.gov/media/137566/download
- Bebtelovimab: https://www.fda.gov/media/156152/download
- Molnupiravir: https://www.fda.gov/media/155054/download

Fact Sheets for Patients:

- Paxlovid: https://www.fda.gov/media/155051/download
- Remdesivir: https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_patient_pi.pdf, https://www.fda.gov/media/137565/download
- Bebtelovimab: https://www.fda.gov/media/156153/download
- Molnupiravir: https://www.fda.gov/media/155055/download
- FDA Patient information: **https://www.fda.gov/consumers/consumer-updates/know-your-treatment-options-covid-19**

Resources- Clinician Webinars

CDC/IDSA COVID-19 Clinician Calls

- https://www.idsociety.org/covid-19-real-time-learning-network/CDC-IDSA-COVID-19-Clinician-Calls/
  - April 11, 2022- All About Paxlovid; Plus Variants Update
  - March 18, 2022- The Latest on COVID-19 Treatment; Plus Variants Update
  - February 28, 2022- Update on Serology Testing
  - February 7, 2022- Outpatient Therapeutics: Addressing Operational Barriers to Delivery & Access; Omicron Update

CDC Clinician Outreach and Communication Activity (COCA)

- https://emergency.cdc.gov/coca/
  - COCA Call: May 5, 2022: Evaluating and Supporting Patients Presenting with Cognitive Symptoms Following COVID
  - COCA Now: April 4, 2022: New COVID-19 Test to Treat Initiative and Locator Tool
  - COCA Now: March 25, 2022: New CDC COVID-19 Quarantine and Isolation (Q&I) Calculator
  - COCA Now: February 24, 2022: Updated List of High-Risk Medical Conditions for Severe COVID-19 Outcomes
  - COCA Call: February 24, 2022: Updated Guidance for Clinicians on COVID-19 Vaccines
  - COCA Call: February 10, 2022: COVID-19 Updates: What Clinicians Need to Know About Multisystem Inflammatory Syndrome in Children
  - COCA Now: February 01, 2022: Ivermectin Products are Not Approved by FDA to Prevent or Treat COVID-19
  - COCA Now: January 31, 2022: How to Talk with Parents and Caregivers about COVID-19 Vaccination
  - COCA Call: January 13, 2022: Updates to CDC's COVID-19 Quarantine and Isolation Guidelines in Healthcare and Non-healthcare Settings
  - → COCA Call: January 12, 2022: What Clinicians Need to Know About the New Oral Antiviral Medications for COVID-19
    - https://emergency.cdc.gov/coca/ppt/2022/011222_slide.pdf

Details for each COVID-19 Therapeutic

Evusheld- Pre-Exposure Prophylaxis

Long-Acting Monoclonal Antibody

EUA for Pre-exposure prophylaxis (prevention) of COVID-19 in certain adults and pediatric patients (12+ and weighing at least 40 kg) who do not have current infection or recent exposure and

- who have moderate-to-severe immune compromise due to a medical condition or who have received immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination **or**
- for whom vaccination with any available approved or authorized COVID-19 vaccine is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).

Activity against Omicron

- Retained activity against Omicron BA.1 and BA.1.1 [1]
- Reduced viral burden and limited inflammation in lungs for all three variants BA.1, BA.1.1, BA.2 [2]

1. Case, J et al. Resilience of S309 and AZD7442 monoclonal antibody treatments against infection by SARS-CoV-2 Omicron lineage strains. Available at https://www.biorxiv.org/content/10.1101/2022.03.17.484787v1 [Last accessed March 2022]
2. Fajnzylber, J et al. SARS-CoV-2 viral load is associated with increased disease severity and mortality. Available at https://www.nature.com/articles/s41467-020-19057-5/ [Last accessed March 2022}

Evusheld Dosage and Administration

Initial Dose: 300 mg Tixagevimab and 300 mg of Cilgavimab

Administered as 2 separate consecutive IM injections

Dosing for Individuals Who Initially Received 150 mg of Tixagevimab and 150 mg Cilgavimab

For individuals who initially received 150 mg tixagevimab and 150 mg cilgavimab:

- Initial dose ≤3 months prior: 150 mg tixagevimab and 150 mg cilgavimab.
- Initial dose >3 months prior: 300 mg Tixagevimab and 300 mg cilgavimab

Repeat dose: The SARS-CoV-2 variants that will be circulating in the United States when EVUSHELD may need to be re-dosed are not known at this time and therefore repeat dosing recommendations cannot be made; the Fact Sheets will be revised with repeat dosing recommendations in the future when more data are available.

Prior to 2/24/22, Evusheld had EUA authorization, at lower dose of 150mg Tixagevimab and 150 mg Cilgavimab. On 2/24/22, FDA adjusted recommendations. Based on data during Omicron Surge, Evusheld was found to be less active against certain Omicron subvariants. Dosing regimen was increased because available data indicated that higher dose of may prevent infection of COVID-19 Omicron subvariants BA.1 and BA.1.1 than the originally authorized Evusheld dose.

Contraindications and Risks and use in Specific Populations

Contraindication:

- **Individuals with previous severe hypersensitivity reactions, including anaphylaxis to any component of EVUSHELD**

Warnings and Precautions:

- **Hypersensitivity including anaphylaxis**
- **Clinically significant bleeding disorders (since IM injection, give with caution to individuals with thrombocytopenia or any coagulation disorder)**
- Cardiovascular Events
  - A higher proportion of subjects who received EVUSHELD versus placebo reported myocardial infarction and cardiac failure serious adverse events. All of the subjects with events had cardiac risk factors and/or a prior history of cardiovascular disease at baseline. A causal relationship between EVUSHELD and these events has not been established. Consider the risks and benefits prior to initiating EVUSHELD in individuals at high risk for cardiovascular events and advise individuals to seek immediate medical attention if they experience any signs or symptoms suggestive of a cardiovascular event.

Adverse Reactions:

- The most common adverse events are headache, fatigue and cough.

Use in Specific Populations:

Pregnancy

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. EVUSHELD should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

Lactation

There are no available data on the presence of tixagevimab or cilgavimab in human milk or animal milk, the effects on the breastfed infant, or the effects of the drug on milk production. Maternal IgG is known to be present in human milk.

1) Nirmatrelvir + Ritonavir (Paxlovid)

EUA 12/22/22 for:

- Treatment of mild-to-moderate COVID-19 in adults & pediatric patients (+ lab confirmed)
- 12 years of age and older weighing at least 40 kg
- And who are at high risk for progression to severe COVID-19, including hospitalization or death
- May be used regardless of vaccination status

NOT authorized for:

- *Patients requiring hospitalization*
- *< age 12, < 40 kg*
- *Pre-exposure or post-exposure treatment*
- *Use for longer than 5 days*

Dose:

Normal renal function (eGFR 60+):

two 150 mg tab Nirmatrelvir & i 100 mg tab of ritonavir PO BID
(with or without food, high fat meal increases nirmatrelvir absorption by 15%)

Impaired renal function, eGFR: 30-60:

One 150 mg tab Nirmatrelvir & one Ritonavir PO BID

New Dose pack coming soon. If not yet available, can ask patient to take one 150mg nirmatrelvir with one 100 mg ritonavir PO BID x 5 days

Possible Side Effects:

Dysgeusia (altered taste) (6% compared to placebo < 1%), diarrhea (3% vs 2%), hypertension (1% vs <1%), myalgia (1% vs < 1%) , muscle aches

Contraindications

- eGFR < 30, severe hepatic impairment (Child-Pugh Class C)
- Co-administration with drugs highly dependent on CYP3A for clearance or potent CYP3A inducers

*eGFR calculated using CKD-Epi formula

1) Nirmatrelvir + Ritonavir (Paxlovid)

Warnings/Precautions

- Drug-Drug Interaction
  - CYP3A inhibitor and can increase medications metabolized by CYP3A
  - Medications that inhibit or induce CYP3A may increase or decrease Paxlovid concentrations
  - These interactions can lead to
  - clinically significant adverse reactions, including fatal events
  - loss of therapeutic effect of Paxlovid and possible viral resistance from decreased Paxlovid exposure
- Allergic reactions/hypersensitivity have been reported- if any allergic reaction/hypersensitivity- immediately discontinue, provider should treat accordingly
- Hepatotoxicity has occurred in patients receiving ritonavir
- HIV-1- Use of Paxlovid may lead to risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled, undiagnosed HIV-1 infection
- The Liverpool COVID-19 Drug Interactions website, and the EUA fact sheet for ritonavir-boosted nirmatrelvir can be used to identify and manage drug-drug interactions

Special Populations

Hepatic Impairment

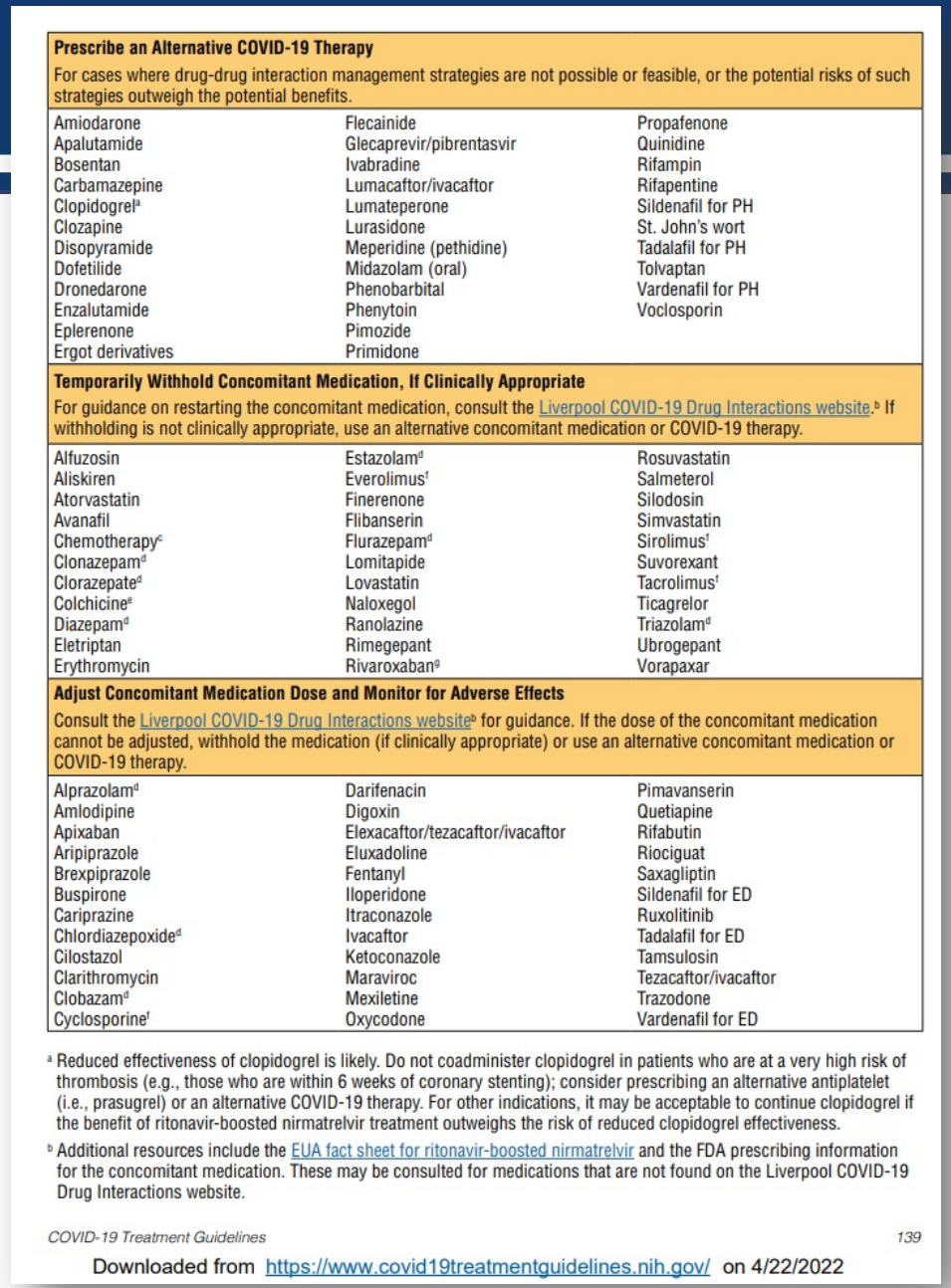
- No dosage adjustment needed for mild/moderate hepatic impairment.
- For **Severe hepatic impairment (Child-Pugh Class C, paxlovid is NOT recommended** due to lack of pharmacokinetic and safety data for nirmatrelvir or ritonavir in that population

Pregnancy and Lactation-

- **No available clinical data on use in pregnancy or with breastfeeding**
- Animal studies- reduced fetal body weights seen at ~10x the nirmatrelvir exposure seen in humans with the authorized dose; no other adverse developmental effects were seen.

Pediatrics

- **No available clinical data in children.** The authorized adult dose is expected to result in comparable serum exposures in patients 12 years of age and older and weighing at least 40 kg.



Prescribe an Alternative COVID-19 Therapy

For cases where drug-drug interaction management strategies are not possible or feasible, or the potential risks of such strategies outweigh the potential benefits.

Amiodarone	Flecainide	Propafenone
Apalutamide	Glecaprevir/pibrentasvir	Quinidine
Bosentan	Ivabradine	Rifampin
Carbamazepine	Lumacaftor/ivacaftor	Rifapentine
Clopidogrel[a]	Lumateperone	Sildenafil for PH
Clozapine	Lurasidone	St. John's wort
Disopyramide	Meperidine (pethidine)	Tadalafil for PH
Dofetilide	Midazolam (oral)	Tolvaptan
Dronedarone	Phenobarbital	Vardenafil for PH
Enzalutamide	Phenytoin	Voclosporin
Eplerenone	Pimozide	
Ergot derivatives	Primidone	

Temporarily Withhold Concomitant Medication, If Clinically Appropriate

For guidance on restarting the concomitant medication, consult the Liverpool COVID-19 Drug Interactions website.[b] If withholding is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy.

Alfuzosin	Estazolam[d]	Rosuvastatin
Aliskiren	Everolimus[f]	Salmeterol
Atorvastatin	Finerenone	Silodosin
Avanafil	Flibanserin	Simvastatin
Chemotherapy[c]	Flurazepam[d]	Sirolimus[f]
Clonazepam[d]	Lomitapide	Suvorexant
Clorazepate[d]	Lovastatin	Tacrolimus[f]
Colchicine[e]	Naloxegol	Ticagrelor
Diazepam[d]	Ranolazine	Triazolam[d]
Eletriptan	Rimegepant	Ubrogepant
Erythromycin	Rivaroxaban[g]	Vorapaxar

Adjust Concomitant Medication Dose and Monitor for Adverse Effects

Consult the Liverpool COVID-19 Drug Interactions website[b] for guidance. 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.

Alprazolam[d]	Darifenacin	Pimavanserin
Amlodipine	Digoxin	Quetiapine
Apixaban	Elexacaftor/tezacaftor/ivacaftor	Rifabutin
Aripiprazole	Eluxadoline	Riociguat
Brexpiprazole	Fentanyl	Saxagliptin
Buspirone	Iloperidone	Sildenafil for ED
Cariprazine	Itraconazole	Ruxolitinib
Chlordiazepoxide[d]	Ivacaftor	Tadalafil for ED
Cilostazol	Ketoconazole	Tamsulosin
Clarithromycin	Maraviroc	Tezacaftor/ivacaftor
Clobazam[d]	Mexiletine	Trazodone
Cyclosporine[f]	Oxycodone	Vardenafil for ED

[a] Reduced effectiveness of clopidogrel is likely. Do not coadminister clopidogrel in patients who are at a very high risk of thrombosis (e.g., those who are within 6 weeks of coronary stenting); consider prescribing an alternative antiplatelet (i.e., prasugrel) or an alternative COVID-19 therapy. For other indications, it may be acceptable to continue clopidogrel if the benefit of ritonavir-boosted nirmatrelvir treatment outweighs the risk of reduced clopidogrel effectiveness.

[b] Additional resources include the EUA fact sheet for ritonavir-boosted nirmatrelvir and the FDA prescribing information for the concomitant medication. These may be consulted for medications that are not found on the Liverpool COVID-19 Drug Interactions website.

From NIH COVID19 Treatment Guidelines (updated 4/22/22)- page 139- this table is NOT a comprehensive list!

Data on Efficacy: EPIC-HR, continued

Efficacy Results in Non-Hospitalized Adults with COVID-19 Dosed within 5 Days of Symptom Onset who Did Not Receive COVID-19 mAb Treatment at Baseline

	PAXLOVID™ (N=1,039)	PLACEBO (N=1,046)
Primary endpoint: COVID-19 related hospitalization or death from any cause through Day 28, n(%)	8 (.08%)	66 (6.3%)
Reduction relative to placebo for primary endpoint[a] [95%, CI], %	-5.62 (-7.21,-4.03)	
All-cause mortality through Day 28, %	0	12 (1.1%)

a. The estimated cumulative proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.

- **88% (95% CI: 75%, 94%)** relative risk reduction for the primary endpoint (proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28)
- Treatment effect was generally consistent across subgroups, including baseline serology status.

1) Nirmatrelvir + Ritonavir (Paxlovid)

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	**Adverse Events**	**Monitoring Parameters**	**Drug-Drug Interaction Potential**	**Comments and Links to Clinical Trials**
Ritonavir-Boosted Nirmatrelvir (Paxlovid) *Authorized under FDA EUA for the treatment of mild to moderate COVID-19 in high-risk individuals aged ≥12 years and weighing ≥40 kg.*				
EUA Dose for COVID-19[1] *Dosing Based on eGFR:* • ≥60 mL/min: Nirmatrelvir 300 mg (two, 150-mg tablets) with RTV 100 mg (one, 100-mg tablet) twice daily for 5 days • ≥30 to 60 mL/min: Nirmatrelvir 150 mg (one, 150-mg tablet) with RTV 100 mg (one, 100-mg tablet) twice daily for 5 days • <30 mL/min: Not recommended	• Dysgeusia • Diarrhea • HTN • Myalgia	• Monitor for potential AEs due to drug-drug interactions with concomitant medication(s). • Use with caution in patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis.	• RTV-boosted nirmatrelvir has significant and complex drug-drug interactions. Before prescribing RTV-boosted nirmatrelvir, **carefully review concomitant medications**, including OTC medicines, herbal supplements, and recreational drugs. See Ritonavir-Boosted Nirmatrelvir (Paxlovid) for more information.	• Both nirmatrelvir and RTV tablets can be taken with or without food.
Dosing for Patients with Severe Hepatic Impairment (Child-Pugh Class C): • Not recommended			• Consult the EUA fact sheet for Paxlovid, the Liverpool COVID-19 Drug Interactions website, and Table A in Ritonavir-Boosted Nirmatrelvir (Paxlovid) to identify and manage drug-drug interactions.	

From NIH COVID-19 Treatment Guidelines uploaded 4/25/22, page 192-3: Coronavirus Disease 2019 (COVID-19) Treatment Guidelines (nih.gov)

Drug Interactions, continued

As a healthcare provider, you should:

- **Inform patients that Paxlovid™ may interact with some drugs and is contraindicated for use with some drugs**
- **Obtain a complete medication list from your patient (including nonprescription drugs and herbals)**
- **Check for clinically significant drug interactions:**
  - Section 7.3 of the EUA Fact Sheet: https://www.fda.gov/media/155050/download
  - NIH Statement on Paxlovid™ Drug-Drug Interactions: https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-paxlovid-drug-druginteractions/
  - https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/management-of-drug-interactions-with-nirmatrelvirritonavir-paxlovid/
  - https://www.covid19-druginteractions.org/checker

- **Based on the drug interactions, decide if:**
  - Paxlovid™ use is appropriate versus an alternative authorized treatment
  - If appropriate, whether your patient should hold, change, or dose-reduce other medications while taking Paxlovid™, or if additional monitoring may be needed

Paxlovid™ Summary

- Paxlovid™ was authorized on 12/22/21 for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older and ≥40 kg) who are at high risk for progression to severe COVID-19*.
- Paxlovid™ reduced COVID-19 related hospitalization and death by 88% when given within 5 days of symptom onset, without concerning safety findings, in the clinical trial EPIC-HR.
- Key Things to Remember When Prescribing:
  - Multiple drug interactions
  - Reduced dose for moderate renal impairment
  - Not recommended with severe renal impairment or severe hepatic impairment

*Paxlovid™ may be used regardless of COVID-19 vaccination status under EUA

What about COVID-19 Rebound after Paxlovid Treatment

CDC Health Advisory May 24, 2022

https://emergency.cdc.gov/han/2022/han00467.asp

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.

Recommendations for Healthcare Providers

For patients with COVID-19 rebound

- There is currently no evidence that additional treatment for COVID-19 is needed for COVID-19 rebound. Based on data available at this time, patient monitoring continues to be the most appropriate management for patients with recurrence of symptoms after completion of a treatment course of Paxlovid.
- Advise people with COVID-19 rebound to follow CDC's guidance on isolation and take precautions to prevent further transmission. Patients should re-isolate for at least 5 days. Per CDC guidance, they can end their re-isolation period after 5 full days if fever has resolved for 24 hours (without the use of fever-reducing medication) and symptoms are improving. The patient should wear a mask for a total of 10 days after rebound symptoms started.
- Consider clinical evaluation of patients who have COVID-19 rebound and symptoms that persist or worsen.
- Healthcare providers are encouraged to report cases of COVID-19 rebound to Pfizer after Paxlovid treatment using the following online tool: Pfizer Safety Reportingexternal icon and to FDA MedWatch. Complete and submit a MedWatch formexternal icon, or complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178). Call 1-800-FDA-1088 for questions.

2) Remdesivir- (Veklury)

- **Adenosine nucleotide analogue prodrug**
- **Broad-spectrum against several RNA viruses**

FDA: (updated April 25, 2022)

- Treatment of COVID-19 in individuals aged 28 days of age or older, weighing at least 3 kg (7 lbs) with positive results of direct SARS-CoV-2 viral testing who are
- hospitalized or,
- not hospitalized and have mild-to-moderate COVID-19 and are at high risk for progression to severe COVID-19, including hospitalization or death.

Dose:

Pediatric 3 kg or less than 40 kg

Single loading dose 5 mg/kg on Day 1 followed by once daily maintenance doses of Veklury 2.5mg/kg from Day 2 via IV.

Adult and Pediatric patients weighing at least 40 kg

Single loading dose of 200 mg on Day 1 followed by once daily maintenance dose 100 mg from day 2 via IV

Duration of treatment

3 days treatment course for Non-Hospitalized patients with mild-moderate COVID 19 at risk for progression to severe COVID-19

10 day treatment course for hospitalized patients requiring invasive mechanical ventilation and/or ECMO

5 days treatment course for hospitalized patients not requiring invasive Mechanical Ventilation and/or ECMO

Possible Side Effects:

Nausea (5%), increased ALT and AST (5%)

Less common adverse reactions: hypersensitivity reactions, seizure, rash

Contraindications

- History of clinically significant hypersensitivity reactions to Veklury or any components of the product

2) Remdesivir (Veklury)

Warnings/Precautions

- Allergic reactions/hypersensitivity have been reported- if any allergic reaction/hypersensitivity- immediately discontinue, provider should treat accordingly
- Increased risk of transaminase elevations. Perform hepatic lab testing in all patients. Consider discontinuing if ALT levels increase > 10x ULN. Discontinue Veklury if ALT elevation is accompanied by signs or symptoms of liver inflammation
- Risk of reduced antiviral activity when co-administered with chloroquine or hydroxychloroquine. Coadministration with chloroquine phosphate or hydroxychloroquine sulfate is not recommended.
- Should not be given to patient with ALT $\geq$ 5x Upper limit of normal or ALT elevation associated with increase conjugated bilirubin, alkaline phosphatase or INR

Special Populations

Renal Impairment

- Not recommended for individuals with eGFR < 30 ml/min

Pregnancy and Lactation-

- **No available clinical data on use in pregnancy or with breastfeeding**

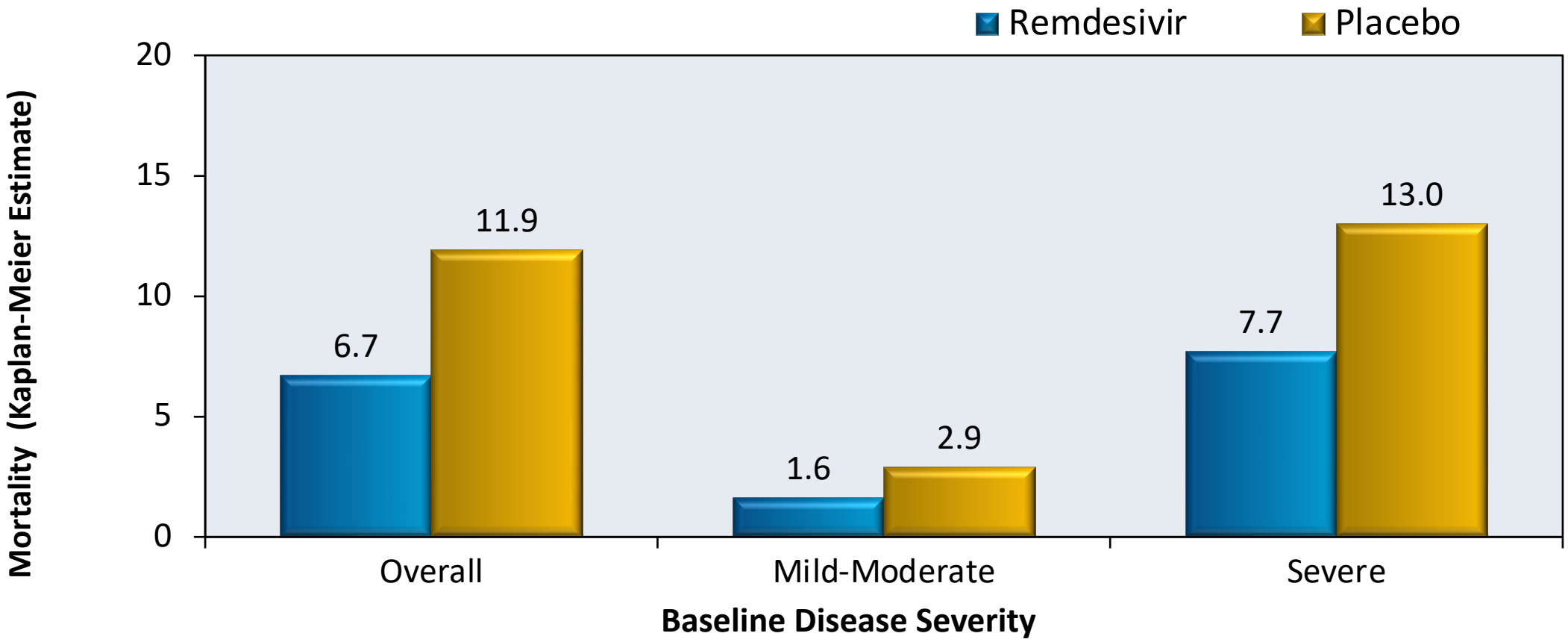
2) Remdesivir- Veklury

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Remdesivir *Approved by the FDA for the treatment of COVID-19 in individuals aged ≥12 years and weighing ≥40 kg.*				

Adults and Children (Aged ≥12 Years and Weighing ≥40 kg):
• RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily from Day 2
Dose Recommended in FDA EUA For Children Weighing 3.5 kg to <40 kg:
• RDV 5 mg/kg IV on Day 1, then RDV 2.5 mg/kg IV once daily from Day 2
• Total Treatment Duration:
  • Nonhospitalized patients: 3 days
  • Hospitalized patients: 5 days or until hospital discharge
	• Nausea
	• ALT and AST elevations
	• Hypersensitivity
	• Increases in prothrombin time
	• Drug vehicle is SBECD, which has been associated with renal and liver toxicity. SBECD accumulation may occur in patients with moderate or severe renal impairment.
	• Each 100 mg vial of RDV lyophilized powder contains 3 g of SBECD, and each 100 mg/20 mL vial of RDV solution contains 6 g of SBECD.
	• Clinicians may consider preferentially using the lyophilized powder formulation (which contains less SBECD) in patients with renal impairment.
		• Monitor patients for infusion reactions during the infusion and observe them for ≥1 hour after the infusion as clinically appropriate.
		• Renal function, hepatic function and prothrombin time as clinically indicated
		• FDA does not recommend using RDV when eGFR is <30 mL/min. See the Remdesivir section for information on using RDV in people with renal insufficiency.
			• Clinical drug-drug interaction studies of RDV have not been conducted.
			• In vitro, RDV is a minor substrate of CYP3A4, and a substrate of OATP1B1, and P-gp and an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1.[2]
				• RDV should be administered in settings in which health care providers have immediate access to medications to treat a severe infusion-related reactions or HSR, such as anaphylaxis, and the ability to activate the emergency medical system.
				• A list of clinical trials is available: Remdesivir

From NIH COVID-19 Treatment Guidelines uploaded 4/25/22, page 193: Coronavirus Disease 2019 (COVID-19) Treatment Guidelines (nih.gov)

2) Remdesivir for the Treatment of Covid-19 (ACTT-1): Results, Mortality by Days 15 and 29 (Kaplan-Meier Estimate)



"Our data show that remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with COVID-19 and had evidence of lower respiratory tract infection."

Source: Beigel JH, et al. N Engl J Med. October 8, 2020. [Online ahead of print]

3) (Alternative Treatment) Bebtelovimab

Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Bebtelovimab (Anti-SARS-CoV-2 Monoclonal Antibody) *Authorized for the treatment of COVID-19 under FDA EUA.*				
Dose Recommended in FDA EUA for Treatment of COVID-19 in Adults and Pediatric Patients Aged ≥12 Years and Weighing ≥40 kg: • BEB 175 mg as an IV injection over at least 30 seconds	• Nausea • Vomiting • Pruritis • Rash • Hypersensitivity, including anaphylaxis and infusion-related reactions	• Only for administration in health care settings by qualified health care providers who have immediate access to emergency medical services and medications to treat severe infusion reactions. • Monitor during IV injection and for ≥1 hour after injection is completed.	• Drug-drug interactions are unlikely between BEB and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers.	**Availability:** • Under the FDA EUA, BEB is available for the treatment of high-risk outpatients with mild to moderate COVID-19.[1] See Anti-SARS-CoV-2 Monoclonal Antibodies for a list of high-risk conditions. • A list of clinical trials is available: Bebtelovimab

https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf **Table 3c, page 228 (updated 4/8/22)**

Third Line alternatives after Paxlovid and Remdesivir

Beptelovimab
Molnupiravir

If **ritonavir-boosted nirmatrelvir, sotrovimab,** or **remdesivir** are not available, feasible to deliver, or clinically appropriate, the Panel recommends using either **bebtelovimab (CIII)** or **molnupiravir (CIIa)**. The Panel's recommendation on bebtelovimab is primarily based on laboratory data showing its potent activity against the Omicron VOC, its BA.1 and BA.2 subvariants, and other VOCs and on limited clinical trial data. The assessment of the clinical efficacy of bebtelovimab is limited to 1 small, Phase 2, randomized, placebo-controlled trial in patients at low risk of disease progression and 1 small randomized controlled trial that compared bebtelovimab to an anti-SARS-CoV-2 mAb combination of bamlanivimab, etesevimab, and bebtelovimab in patients at high risk of disease progression (described below). The MOVe-OUT trial that compared the use of molnupiravir to placebo reported a 30% reduction in rate of hospitalization or death in the molnupiravir recipients, which is markedly lower than the rate reduction reported with the use of ritonavir-boosted nirmatrelvir, sotrovimab, or remdesivir.[4] More detailed information regarding these therapies can be found in Therapeutic Management of Nonhospitalized Adults With COVID-19.

3) Alternative therapy- Bebtelovimab

Drug Class- Monoclonal antibody

- Recombinant neutralizing human mAb that binds to the spike protein of SARS-CoV-2
- broad activity against SARS-CoV-2 variants, including Omicron variant and its BA.1, BA.1.1, BA.2 subvariants

EUA 3/25/22

- Treatment of mild to moderate coronavirus disease 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 how are at high risk for progression to severe COVID-19, including hospitalization or death

NIH panel- recommends using Bebtelovimab 175 mg IV in those age 12+ ONLY when Paxlovid and remdesivir are not available, feasible to use, or clinically appropriate. Treatment should be initiated as soon as possible and within 7 days of symptom onset

Dose:

175 mg/2ml IV over 30 seconds followed by flushing injection line with 0.9% Sodium Chloride

(same for adults and pediatric patients age 12+ weighing at least 40 kg)

Observe x 1 hour after infusion for infusion reaction/hypersensitivity

Contra-Indications:

- Hypersensitivity including anaphylaxis and infusion-related reactions
- Clinical worsening after SARS-CoV-2 Monoclonal Antibody Administration
- Limitations of benefit and potential for Risk in patients with Severe COVID-19

Adverse Reactions:

- Infusion related reactions (0.3%), pruritis (0.3%), rash (0.8%)

Drug Interactions:

- None known (Not renally excreted or metabolized by Cytochrome P450 enzymes)

Iketani S, Liu L, Guo Y, et al. Antibody evasion properties of SARS-CoV-2 Omicron sublineages. Nature. 2022;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35240676

Westendorf K, Zentelis S, Wang L, et al. LY-CoV1404 (bebtelovimab) potently neutralizes SARS-CoV-2 variants. bioRxiv. 2022;Preprint. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33972947

NIH Panel guidance- from Coronavirus Disease 2019 (COVID-19) Treatment Guidelines (nih.gov) page 61

3) Alternative therapeutic- Bebtelovimab

Warnings/Precautions

- Allergic reactions/hypersensitivity reactions including anaphylaxis have been reported- if any allergic reaction/hypersensitivity- immediately discontinue, provider should treat accordingly
- Infusion-related reactions which may occur up to 24 hours after injection
- Signs and symptoms of infusion-related reactions may include:
    - fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vasovagal reactions (e.g., pre-syncope, syncope), dizziness and diaphoresis.
- Clinical worsening after SARS-CoV-2 monoclonal antibody administration
    - Has been reported- may include fever, hypoxia or increased respiratory difficulty, arrhythmia, fatigue, and altered mental status. Some of these events require hospitalization. It is not known if these events were related to the monoclonal antibody use or were due to progression of COVID-19

Special Populations

- Pregnancy/Lactation- insufficient or not data
- Pediatric Use- Not authorized < 12 or weighing < 40 kg. Safety and effectiveness have not been assessed in pediatric patients.
- Geriatric Use- Of 602 patients receiving bebtelovimab in BLAZE-4, 10.5% were 65 years of age and older and 3.3% were 75 years of age and older. No difference in the pharmacokinetics in geriatric patients compared to younger patients.

LIMITATIONS OF AUTHORIZED USE

Bebtelovimab is not authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to this drug and regional variant frequency.

- FDA's determination and any updates will be available at: https://www.fda.gov/emergencypreparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-useauthorization#coviddrugs.

Bebtelovimab is not authorized for use in patients, who:

- are hospitalized due to COVID-19, OR o require oxygen therapy and/or respiratory support due to COVID-19, OR
- require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 and are on chronic oxygen therapy and/or respiratory support due to underlying non-COVID-19 related comorbidity'

Bebtelovimab and activity against other COVID Variants

Table 2: Bebtelovimab Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Spike Protein Variants

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested[a]	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y	No change[b]
B.1.351	South Africa	Beta	K417N + E484K + N501Y	No change[b]
P.1	Brazil	Gamma	K417T + E484K + N501Y	No change[b]
B.1.617.2/AY.3	India	Delta	L452R + T478K	No change[b]
AY.1/AY.2 (B.1.617.2 sublineages)	India	Delta [+K417N]	L452R + T478K + K417N	No change[b]
B.1.427/B.1.429	USA (California)	Epsilon	L452R	No change[b]
B.1.526[c]	USA (New York)	Iota	E484K	No change[b]
B.1.617.1	India	Kappa	L452R + E484Q	No change[b]
C.37	Peru	Lambda	L452Q + F490S	No change[b]
B.1.621	Colombia	Mu	R346K + E484K + N501Y	5.3
B.1.1.529/BA.1	South Africa	Omicron	G339D + S371L + S373P + S375F + K417N + N440K + G446S + S477N + T478K + E484A + Q493R + G496S + Q498R + N501Y + Y505H	No change[b]
BA.1.1	South Africa	Omicron [+R346K]	G339D + R346K + S371L + S373P + S375F + K417N + N440K + G446S + S477N + T478K + E484A + Q493R + G496S + Q498R + N501Y + Y505H	No change[b]
BA.2	South Africa	Omicron [BA.2]	G339D + S371F + S373P + S375F + T376A + D405N + R408S + K417N + N440K + S477N + T478K + E484A + Q493R + Q498R + N501Y + Y505H	No change[b]

[a] Key substitutions occurring in the receptor binding domain of spike protein are listed. Pseudotyped VLP containing the full-length spike protein reflective of the consensus sequence for each of the variant lineages were tested.
[b] No change: <5-fold reduction in susceptibility.
[c] Isolates of the B.1.526 lineage harbor several spike protein amino acid substitutions, and not all isolates contain the E484K substitution (as of February 2021).

Table 3: Authentic[a] SARS-CoV-2 Neutralization Data for Bebtelovimab

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested[b]	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y	No change[c]
B.1.351	South Africa	Beta	K417N, E484K, N501Y	No change[c,d]
P.1	Brazil	Gamma	K417T, E484K, N501Y	No change[c]
B.1.617.2/AY.3	India	Delta	L452R, T478K	No change[c,d]
B.1.427/B.1.429	USA (California)	Epsilon	L452R	No change[c]
B.1.526[e]	USA (New York)	Iota	E484K	No change[c]
B.1.1.529/BA.1	South Africa	Omicron	G339D + S371L + S373P + S375F + K417N + N440K + G446S + S477N + T478K + E484A + Q493R + G496S + Q498R + N501Y + Y505H	No change[c,d]
BA.1.1	South Africa	Omicron [+R346K]	G339D + R346K + S371L + S373P + S375F + K417N + N440K + G446S + S477N + T478K + E484A + Q493R + G496S + Q498R + N501Y + Y505H	No change[c]

[a] The B.1.1.7, B.1.351, B.1.617.2, and B.1.1.529/BA.1 variants were assessed using cell culture-expanded virus isolates and tested using a plaque reduction assay; the B.1.351, P.1, B.1.617.2, B.1.1.529/BA.1 and BA.1.1 variants were assessed using cell culture-expanded isolates and tested using a microneutralization assay with a CPE-based endpoint titer to determine the $IC_{>99}$; the B.1.526/E484K and B.1.427/B.1.429/L452R substitutions were assessed using recombinant SARS-CoV-2 (USA/WA/1/2020 isolate with E484K or L452R) and tested using a plaque reduction assay.
[b] Key substitutions occurring in receptor binding domain of spike protein which are associated with each lineage.
[c] No change: <5-fold reduction in susceptibility when compared to ancestral control isolate using the same methodology.
[d] These viral variants have been tested with two different neutralization methodologies, both yielding <5-fold reductions in susceptibility.
[e] Isolates of the B.1.526 lineage harbor several spike protein amino acid substitutions, and not all isolates contain the E484K substitution (as of February 2021).

From EUA Factsheet for HCP- - (lilly.com)

3) Alternative therapy- Molnupiravir (Lagevrio)

- **Nucleoside analogue that inhibits replication by viral mutagenesis**

EUA

- Treatment of mild-moderate coronavirus disease 2019 (COVID-19) in adults
  - 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.
- *Molnupiravir is not authorized:*
  - for use in patients who are less than 18 years of age
  - for initiation of treatment in patients hospitalized due to COVID-19. Benefit of treatment with LAGEVRIO has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19
  - for use for longer than 5 consecutive days
  - for pre-exposure or post-exposure prophylaxis for prevention of COVID-19

Dose:

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

Possible Side Effects:

diarrhea, nausea, dizziness

Contraindications

- No contraindications have been identified based on limited available data on emergency use (per label)

3) Alternative Therapy- Molnupiravir (Lagevrio)

Warnings/Precautions

- Embryo-Fetal Toxicity: not recommended for use during pregnancy.
- Hypersensitivity reactions, including anaphylaxis have been reported with LAGEVRIO. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue LAGEVRIO.
- Bone and Cartilage Toxicity: LAGEVRIO is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth.

Special Populations

Renal Impairment

- No dosage adjustment in patients with any degree of renal impairment is recommended

Hepatic Impairment

- No dosage adjustments in patients with hepatic impairment is recommended.

Pregnancy

- Not recommended during pregnancy- causes fetal harm- do not use in pregnant individuals
- Advise females of childbearing potential to use effective contraception correctly and consistently, as applicable for the duration of treatment and for 4 days after the last day of treatment. Males of reproductive potential who are 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

Lactation

- Breastfeeding is not recommended during treatment and for 4 days after the last dose. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose.

Trial P002 (MOVe-OUT): Efficacy Results

	Molnupiravir (N=709) n(%)	Placebo (N=699) n(%)	Adjusted Risk Difference % (95%CI)
All-cause hospitalization ≥24 hours for acute care or death through Day 29	48 (6.8%)	68 (9.7%)	-3.0 (-5.9%, -0.1%)
All-cause mortality through Day 29	1 (0.1%)	9 (1.3%)	

*The determination of primary efficacy was based on a planned interim analysis of 762 subjects. At the interim analysis, 7.3% of participants who received molnupiravir were either hospitalized or died through Day 29 (28/385), compared with 14.1% of placebo-treated participants (53/377). The adjusted risk difference was -6.8% with a 95% CI of (-11.3%, -2.4%) and 2-sided p-value = 0.0024.

Adjusted relative risk reduction of molnupiravir compared to placebo for all randomized participants was 30% (95% CI: 1%, 51%).

Analyses are adjusted by the stratification factor of time of COVID-19 symptom onset (≤3 days vs. >3 [4-5] days).

3) Alternative Therapeutic- Molnupiravir

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	**Adverse Events**	**Monitoring Parameters**	**Drug-Drug Interaction Potential**	**Comments and Links to Clinical Trials**
Molnupiravir *Authorized under FDA EUA for the treatment of mild to moderate COVID-19 in high-risk individuals aged ≥18 years.*				
Dose Recommended in FDA EUA: • MOV 800 mg (four, 200-mg capsules) PO every 12 hours for 5 days	• Diarrhea • Nausea • Dizziness • Per the FDA, the 5-day course of MOV has a low risk for genotoxicity.[3] See the Molnupiravir section for details.	• Before initiating MOV, assess pregnancy status as clinically indicated. • Monitor for potential AEs.	• Clinical drug-drug interaction studies of MOV have not been conducted. • Drug-drug interactions related to hepatic metabolism are not expected.	• MOV can be taken with or without food. • Sexually active individuals of reproductive potential should use effective contraception during and following treatment with MOV. See the Molnupiravir section for details. • If MOV is prescribed for a pregnant individual, the prescribing clinician should document that the risks and benefits were discussed and that the patient chose this therapy. Pregnant patients should also be informed of the pregnancy surveillance program and if they agree to participate, be enrolled in the program. See the Molnupiravir section for details. • During MOV treatment and for 4 days after the final dose, lactating people **should not** breastfeed their infants. • MOV is not authorized for use in children aged <18 years due to potential effects on bone and cartilage growth. • A list of clinical trials is available: Molnupiravir

From NIH COVID-19 Treatment Guidelines uploaded 4/25/22, page 194: Coronavirus Disease 2019 (COVID-19) Treatment Guidelines (nih.gov)

3) Alternative Therapeutic- Molnupiravir

- **MOV is not recommended for use during pregnancy**
  - Based on animal data, MOV may cause fetal harm when administered to pregnant individuals

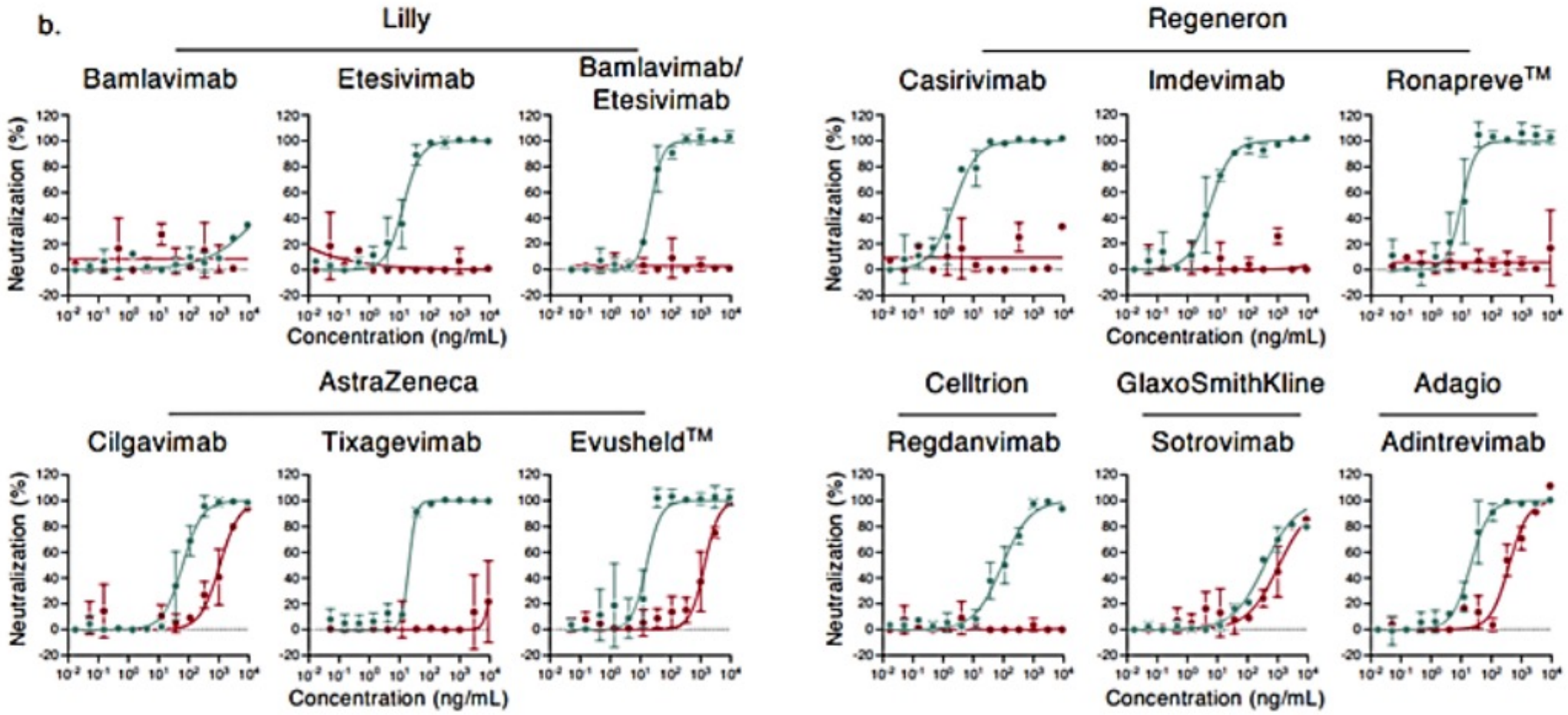
- However, if a healthcare provider determines that the benefits outweigh the risks for an individual pregnant patient, they must:
  - Counsel the patient regarding the known and potential benefits and potential risks of MOV use during pregnancy
  - Document that the patient is aware of the known and potential benefits and potential risks of MOV 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 https://pregnancyreporting.msd.com

3) Molnupiravir- Prescriber Requirements

- Provide an electronic or hard copy of patient fact sheet and document that patient has received an electronic or hard copy of the patient fact sheet
- Review the information contained within the patient factsheet with the patient and counsel patient on the known and potential benefits and risks of MOV
- Assess whether an individual of childbearing potential is pregnant or not, if clinically indicated
- Advise individuals of childbearing potential to use contraception for the duration of treatment and for 4 days after the last dose of MOV
- Advise sexually active individuals with partners of childbearing potential to use contraception during treatment and for at least 3 months after the last dose of MOV
- Make individuals of childbearing potential aware of pregnancy surveillance program
- Report all medication errors and serious adverse events potentially related to MOV within 7 calendar days from the healthcare provider's awareness of the event
  - www.fda.gov/medwatch/report.htm
  - or call 1-800-FDA-1088
- See prior slide for requirements for use in pregnancy

Extra slides/resources

Susceptibility to monoclonal antibodies appears to be lower for Omicron compared to Delta



Considerable escape of SARS-CoV-2 variant Omicron to antibody neutralization: https://www.biorxiv.org/content/10.1101/2021.12.14.472630v1.full.pdf

PRODUCT	MONOCLONAL ANTIBODIES (mAbs)			IV ANTIVIRALS	ORAL ANTIVIRALS	
	Preventative (PrEP)	Treatment		Treatment	Treatment	
	Evusheld (tixagevimab/cilgavimab)	sotrovimab	3 bebtelovimab	2 VEKLURY® (remdesivir)	1 Paxlovid (nirmatrelvir/ritonavir)	3 molnupiravir
Manufacturer	AstraZeneca Pharmaceuticals LP	[illegible]thKline [illegible]hnology	Eli Lilly and Company	Gilead Sciences, Inc.	Pfizer, Inc.	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Date of Latest Update to Emergency Use Authorization (EUA)[2] and Prescribing Information (PI)	EUA: 02/24/22 PI: n/a	[illegible]02/23 [illegible]n/a	EUA: 02/11/22 PI: n/a	EUA: 01/21/22 PI: 01/21/22	EUA: 12/22/21 PI: n/a	EUA: 02/23/22 PI: n/a
Mechanism of Action	mAb against conserved epitope of spike protein; blocks viral entry	mAb agains[illegible] atta[illegible]ocks viral [illegible]ry	mAb against spike protein; blocks viral attachment to host cells	Nucleotide analog ribonucleic acid (RNA) polymerase inhibitor that halts viral replication	Viral protease inhibitor that halts viral replication	Nucleoside analog that inhibits viral replication by viral mutagenesis
Treatment Efficacy per Clinical Trials[3]	77% reduction in developing symptomatic COVID-19	7[illegible] hospi[illegible]aths	Symptomatic improvement and Day 5 reduction in viral load vs. placebo[4]	87% reduction in hospitalizations/deaths[5]	88% reduction in hospitalizations/deaths	30% reduction in hospitalizations/deaths
Activity Against SARS-CoV- 2 Variants[6]	*Omicron variant:* Likely active *Delta variant:* Active *Other variants:* See Section 12.4 of Evusheld Healthcare Provider Fact Sheet	*Omicron varia*[illegible]ive *Delta variant:* A[illegible] *Other variants:* [illegible]n 15 of sotrovimab Hea[illegible]rovider Fact Sheet	*Omicron variant:* Likely active *Delta variant:* Active *Other variants:* See Section 12.4 of bebtelovimab Healthcare Provider Fact Sheet	*Omicron variant:* Likely active[7] *Delta variant:* Active *Other variants:* See Section 15 of remdesivir Healthcare Provider Fact Sheet See Section 12.4 of remdesivir package insert	*Omicron variant:* Likely active[7] *Delta variant:* Active *Other variants:* See Section 12.4 of Paxlovid Healthcare Provider Fact Sheet	*Omicron variant:* Likely active[7] *Delta variant:* Active *Other variants:* See Section 12.4 of molnupiravir Healthcare Provider Fact Sheet
Authorized Use(s)	Pre-exposure prophylaxis (PrEP)	Treatment of m[illegible]te COVID-19	Treatment of mild-moderate COVID-19	Treatment of mild-moderate COVID-19	Treatment of mild-moderate COVID-19	Treatment of mild-moderate COVID-19
Eligible Population(s)	Adult and pediatric patients (at least 12 years of age and older weighing at least 40 kg) who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS CoV-2, and who have moderate to severe immune compromise or for those who any EUA or approved vaccine is not recommended.	Adult and ped[illegible]s (at least 12 years of ag[illegible]eighing at least 40 kg) a[illegible] progressing [illegible]-19, including ho[illegible]eath	Adult and pediatric patients (at least 12 years of age and older weighing at least 40 kg) at high risk[8] for progressing to severe COVID-19, including hospitalization or death, **and** for whom alternative COVID-19 treatment options approved or authorized by the U.S. Food and Drug Administration (FDA) are not accessible or clinically appropriate	**FDA-approved for:** Adults and pediatric patients (12 years of age and older and weighing at least 40 kg) who are (1) hospitalized or (2) not hospitalized and at high risk[8] for progression to severe COVID-19, including hospitalization or death **EUA for:** Pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg who are (1) hospitalized or (2) not hospitalized and at high risk[8] for progression to severe COVID-19, including hospitalization or death	Adults and pediatric patients (12 years of age and older weighing at least 40 kg) at high risk[8] for progressing to severe COVID-19, including hospitalization or death	Adults at high risk[8] for progressing to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate
Prescribing Window	Pre-exposure	Initiate within 7 days of symptom onset	Initiate within 7 days of symptom onset	Initiate within 7 days of symptom onset	Initiate within 5 days of symptom onset	Initiate within 5 days of symptom onset

Generic Name	Tixagevimab/Cilgavimab (Evusheld), PrEP	1 Nirmatrelvir/ritonavir (Paxlovid) Oral	2 Remdesivir (Veklury) IV	3 Bebtelovimab IV	3 Molnupiravir (Lagevrio) Oral
Manufacturer	AstraZeneca	Pfizer	Gilead	Eli Lilly and Company	Merck
FDA EUA Date	2/24/22	EUA 12/22/21	4/25/22- No longer on EUA- Fully Authorized for Pediatrics 28 days and older, and at least 3 kg (7lbs)	EUA 3/25/22	EUA 12/23/21
Drug Type/Class/MOA	Monoclonal Antibody (mAb) mAb against conserved epitope of spike protein; blocks viral entry	Antiviral Viral protease inhibitor (Nirmatrelvir) and HIV protease inhibitor & CYP3A inhibitor (ritonavir). Halts viral replication	Antiviral Nucleoside analog (RNA) polymerase inhibitor that halts viral replication	Monoclonal Antibody (mAb) mAb against spike, blocks viral attachment to host cells	Antiviral Nucleoside Analog that inhibits viral replication by viral mutagenesis
Reported efficacy data	77% reduction in developing symptomatic COVID-19	88% reduction in hospitalizations/deaths	87% reduction in hospitalizations/deaths	Symptomatic improvement and Day 5 reduction in viral load vs placebo	30% reduction in hospitalization/deaths
Indication	Pre-Exposure Prophylaxis for those with moderate to severe immunocompromise or for those who any EUA or approved vaccine is not recommended. Individual should not currently be infected or have recent exposure	Treatment mild-moderate COVID for at risk patients			
			Treatment of Hospitalized pt with COVID		
Age/weight requirement	12+ (minimum 40 kg or 88 lb)	12+ (minimum 40 kg or 88 lb)	> 28 days old (min 3.5 kg, 7lb), > 12 years of age (minimum 40 kg, 88lbs)	12+ (minimum 40 kg or 88 lb)	18+
Rx window	PreExposure Period for eligible individual	Within 5 days symptoms onset	Within 7 days symptom onset	Within 7 days symptom onset	Within 5 days symptom onset
Duration of therapy		**5 days**	**3 days** -not hospitalized, mild-mod COVID-10. **5 days** –hospitalized, not on mech vent/ECMO (extend to **10 days** if not improving) **10 days** -hospitalized, on mech vent/ECMO	**1 Time dose**	**5 days**
Testing Requirements **And lab considerations**	none	Positive direct SARS-CoV 2 viral test	Positive direct SARS-CoV 2 viral test Baseline renal function required under EUA for pediatric patients As clinically appropriate- perform renal/hepatic lab testing, assess PTT	Positive direct SARS-CoV 2 viral test	Positive direct SARS-CoV 2 viral test
History requirements **Family planning**	Not specified	Not specified Ritonavir may reduce efficacy of combined hormonal contraceptives. Pt should use effective alternative contraceptive method or additional barrier method of contraception	Not specified	Not specified	**Assess pregnancy status-** not recommended during pregnancy, if childbearing potential, advise of potential risk to fetus, use reliable contraception correctly and consistently for duration of treatment and 4 days after last dose. Males of reproductive potential should use reliable contraception correctly/consistently x 3 months after last dose.

Adapted from https://aspr.hhs.gov/COVID-19/Therapeutics/Documents/side-by-side-overview.pdf

Generic Name	Tixagevimab/Cilgavimab (Evusheld), PrEP	1 Nirmatrelvir/ritonavir (Paxlovid) Oral	2 Remdesivir (Veklury) IV	3 Bebtelovimab IV	3 Molnupiravir (Lagevrio) Oral
Dose	300 mg of tixagevimab (100 mg/mL) and 300 mg of cilgavimab (100 mg/mL) via two separate 3.0 mL consecutive intramuscular (IM) injections of each product. *Patients who received previously (150 mg of tixagevimab and 150 mg of cilgavimab) should receive a second dose (150 mg of tixagevimab and 150 mg of cilgavimab) as soon as possible. The SARS-CoV-2 variants circulating in the US when Evusheld may need to be redosed are not known at this time, therefore, repeat dosing recommendations cannot be made.* **Dosing for Special Population:** **Pediatric patients at least 12 years or older**, and weighing at least 40 kg: no dosage adjustment **Pregnancy or Lactation** - No dosage adjustment **Geriatrics**: No dosage adjustment **Renal:** No dosage adjustment **Hepatic:** Not specified	300 mg nirmatrelvir with 100 mg ritonavir Take all 3 tablets PO BID with or without food *(although eating with fatty meal enhances absorption)* **Dosing for Special Population:** **Pediatric patients** 12+ and at least 40 kg: no dosage adjustment **Pregnancy or Lactation:** No dosage adjustment **Renal:** Normal- mild renal impairment eGFR > 60 mL/min: No dosage **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. **Severe renal impairment, eGFR < 30- ml/min- Not recommended** **Hepatic-** Mild/moderate impairment**:** No dosage adjustment **Severe Impairment, Child-Pugh Class – C- Avoid**	Adults/Peds 12+ at least 40 Kg: Single loading dose 200mg Day 1 IV, then maintenance daily dose 100mg IV **Dosing for Special Population:** **Peds > 28 days, and > 3 kg, < 40kg:** Single Loading dose: 5 mg/kg IV Maintenance dose: 2.5 mg/kg IV **Renal:** **Severe renal impairment eGFR < 30: Not recommended** **28+ day old full term neonate with serum creatinine greater than or equal to 1mg/dL- Not recommended**	175 mg/2ml (87.5 mg/ml) administered via IV injection over 30 seconds **Dosing for Special Population:** **Pediatrics:** If eligible, no dosage adjustment **Pregnancy or Lactation:** No dosage adjustment **Geriatrics:** No dosage adjustment **Renal:** No dosage adjustment **Hepatic:** No dosage adjustment for mild hepatic impairment	800 mg PO q 12 hours (4 capsules per dose) With or without food **Dosing for Special Population:** **Pediatrics:** Not eligible, as it may affect bone and cartilage growth. **Pregnancy or Lactation:** Not recommended for use during pregnancy. Breastfeeding not recommended during treatment or for 4 days after final dose. **Renal:** No dosage adjustment **Hepatic:** No dosage adjustment
How supplied	One carton has Two vials - 150mg/1.5 ml Tixagevimab - 150mg/1.5 ml Cilgavimab	5 daily dose blister cards *renal impairment lower dose packs available	Single Dose Vial 100 mg Remdesivir as lyophilized powder in single dose vial (no reconstituted) 100mg/20ml (5mg/ml) after reconstitution.	Single Dose Vial	Bottle (40 capsules)
Administration details	Administer the IM injections at different injections sites (preferably one in each gluteal muscle, one after the other) For 300mg tixagevimab and 300 mg cilgavimab dose- ensure that the administration sites are appropriate for the volume (3ml per injection) **Monitor for 1 hour** after injection for hypersensitivity	Ok to take with or without food, but high fat meal increases absorption 15%, pills cannot be crushed	Reconstitute powder by adding 19 ml sterile water. see recommended dilution instructions in package insert. **Monitoring recommended 1 hour after infusion**- for hypersensitivity reaction or infusion reaction	Administer entire contents via IV injection over at least 30 seconds. See recommended storage/handling instructions in package insert. **Monitoring recommended 1 hour after infusion**- for hypersensitivity reaction or infusion reaction	Ok to take with or without food, pills cannot be crushed
Adverse Events (if from clinical trials, incidence ≥ 1%)	Injection site reactions 1%: one case of anaphylaxis in clinical trial Headache 6%, fatigue 4%, cough 3%, insomnia 1%, dizziness 1% Injection site reaction 1% Cardiac serious adverse events: 0.6% vs 2% in Evusheld and placebo groups respectively	Dysguesia (altered taste sensation) 6%, diarrhea 3%, hypertension 1%, myalgia 1%	Nausea 10.8%, Headache 5.7%, Cough 3.6%, diarrhea 3.9%, dyspnea 2.5%, fatigue 3.6%, ageusia 2.9%, anosmia 3.2%, dizziness 1.8%, chills 2.2% Lab abnormalities: (10.8%)	Infusion-related: 0.3%, pruritis 0.3%, rash 0.8% Nausea 0.8%, vomiting 0.7%	Diarrhea 2%, nausea 1%, dizziness 1% Lab abnormality: ALT, AST, creatinine, lipase, hemoglobin, platelets, leukocytes- < 2% Post auth experience: Hypersensitivity: anaphylaxis, angioedema Skin disorder: Erythema, rash, urticaria

Generic Name	Tixagevimab/Cilgavimab (Evusheld), PrEP	1 Nirmatrelvir/ritonavir (Paxlovid) Oral	2 Remdesivir (Veklury) IV	3 Bebtelovimab IV	3 Molnupiravir (Lagevrio) Oral
Potential Drug-Drug Interactions	Unlikely	Moderate/High- see prescribing information	Low- See prescribing information	unlikely	None identified
Renal Dose Adjustment		For eGFR 30-60, lower dose advised, not recommended for those with eGFR < 30 ml/min	Not recommended for those with eGFR < 30 ml/min	none	None
Hepatic Dose Adjustment		Avoid in severe hepatic impairment (Child-Pugh Class C)	None- but should monitor LFT pre and during treatment	none	none
Contraindications	Previous severe hypersensitivity reactions, including anaphylaxis to any components of Evusheld	Hypersensitivity to ingredients CYP3A4 drug-drug interactions	Hypersensitivity to Veklury or any of its components	none listed	None listed *Not recommended for use in pregnancy- see special populations
Warnings/drug interactions		Beware of drug interactions, hepatoxicity, HIV-1 drug resistance in patients with HIV-1 infection Many drug interactions (statins, blood thinners, OCP, seizure medications, St. John's Wort) should use drug interaction checker tool		Possible hypersensitivity/infusion related reaction. Clinical worsening after SARs-CoV-2 administration	Embryo-fetal toxicity, bone and cartilage toxicity- not recommended for patients < 18 because of potential effects on bone/cartilage growth Not recommended for use during pregnancy. No drug interactions identified to date Hypersensitivity reactions
Special Populations	Insufficient data in pregnancy or breastfeeding.	No human data on use in pregnancy or breastfeeding	Insufficient human data on use during pregnancy or breastfeeding	Insufficient human data on use during pregnancy or breastfeeding	Not recommended in pregnancy. Not recommended if breastfeeding (has pregnancy surveillance program)
cost	$200 administration fee	$530 per course	$390-520 per dose, or $2,340-3,120 for 5 day tx (hospital)	$ 1,250 per dose	$712 per course

Resources

Generic Name	Tixagevimab/Cilgavimab (Evusheld), PrEP	1 Nirmatrelvir/ritonavir (Paxlovid) Oral	2 Remdesivir (Veklury) IV	3 Bebtelovimab IV	3 Molnupiravir (Lagevrio) Oral
FDA	EUA for PrEP COVID-19	EUA for treatment of mild-moderate COVID-19 Illness	FDA approved for treatment of COVID-19	EUA for treatment of mild-moderate COVID-19 Illness	EUA for treatment of mild-moderate COVID-19 Illness
Activity against Omicron	Other variants: See Section 12.4 of https://www.fda.gov/media/154701/download	Other variants: See Section 12.4 of https://www.fda.gov/media/155050/download	Other Variants- see section 15 of https://www.fda.gov/media/137566/download see section 12.4 of https://www.gilead.com/-/media/files/pdfs/medicines/COVID-19/veklury/veklury_pi.pdf	Other variants: See Section 12.4 of https://www.fda.gov/media/156152/download	other variants: See Section 12.4 of https://www.fda.gov/media/155054/download
Product Website	https://www.evusheld.com/	https://www.covid19oralrx.com/	https://www.gilead.com/remdesivir	http://www.lillyantibody.com/bebtelovimab	https://www.molnupiravir-us.com/patients/
FDA Factsheets for HCP	https://www.fda.gov/media/154701/download	https://www.fda.gov/media/155050/download	https://www.fda.gov/media/137566/download	https://www.fda.gov/media/156152/download	https://www.fda.gov/media/155054/download
FDA Factsheets for patients, parents, caregivers	https://www.fda.gov/media/154702/download	https://www.fda.gov/media/155051/download	https://www.fda.gov/media/137565/download	https://www.fda.gov/media/156153/download	https://www.fda.gov/media/155055/download

Adapted from ASPR HHS Side by Side Overview of Therapeutics Authorized or Approved for the Prevention of COVID-19 Infection or Treatment of Mild-Moderate COVID-19 : Side-by-Side Overview of Outpatient Therapies Authorized for Treatment of Mild-Moderate COVID-19 (hhs.gov)

Remdesivir study NEJM: https://www.nejm.org/doi/full/10.1056/NEJMoa2116846

Study showing maintained in vitro potency Molnupiravir and Remdesivir against Omicron Variant: https://www.biorxiv.org/content/10.1101/2022.01.17.476685v1

Monoclonal Antibody- Infographic and Toolkit: https://www.cms.gov/files/document/covid-infographic-coverage-monoclonal-antibody-products-treat-covid-19.pdf https://www.cms.gov/monoclonal

https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/covid-19-vaccines-and-monoclonal-antibodies
https://www.hrsa.gov/CovidUninsuredClaim