San Francisco Department of Public Health

Guidance

Provider Guidance on the use of Outpatient COVID-19 Therapeutics

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This guidance document was developed by the San Francisco Department of Public Health (SFDPH) for local use.

AUDIENCE: Clinical prescribing providers in San Francisco.

PURPOSE: To guide clinicians in prescribing available outpatient therapies for treatment and prevention of COVID-19.

BACKGROUND: Outpatient therapeutics are available in San Francisco. Therapies to treat COVID-19 help mild to moderately symptomatic non-hospitalized individuals with COVID-19, who are at higher risk of progressing to severe disease. A higher risk of disease progression includes those who are not vaccinated, are not up to date with vaccination, or are not expected to mount sufficient vaccine response. Therapies to prevent COVID-19 infection provide the greatest benefit to those who cannot receive the vaccine due to severe allergic reactions or who have an immune compromise that may limit their response to the vaccine. With improved supply, expanded eligibility for medications now includes many common conditions. This guide was created to help providers prescribe these therapies.

The following guidelines have been adapted from those utilized and shared throughout the San Francisco Health Network and based on the performance of therapies against current variants. Individual provider or practice may adjust their evaluation and prescribing practices based on changing conditions of the disease.

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Recommended patient criteria for outpatient COVID-19 Therapeutics

1. Recently diagnosed with symptomatic COVID-19 AND
2. Mild or moderate disease NOT requiring hospitalization AND
3. At risk for progression to severe COVID-19, due to one of the following:
    a. Age 50 and older, especially those 65 and older
    b. Under age 50 with risk factors for severe disease
    c. Immunocompromised
    d. Unvaccinated or not completely vaccinated
    e. Pregnant

Available Therapies

For Treatment: The following therapies in Table 1 can be considered for mild to moderately *symptomatic* non-hospitalized individuals with COVID-19 at risk of progression to severe disease. Of note, individuals who are hospitalized for a non-COVID indication and who meet these criteria may also be considered for these treatments. See table 1 for the mechanism of action, administration instructions, evidence for efficacy, and clinical considerations for each treatment. The NIH and CDC have ranked them in terms of first-line and second-line therapies. Recommendations for isolation with COVID-19 infection do not change if a patient is given a COVID-19 therapy.

Interim Advisory:

- The FDA (March 2022) began limiting use of Sotrovimab in regions where the BA.2 Omicron subvariant is dominant due to decreased efficacy. California, which is in HHS region 9, surpassed this threshold on March 30th. Therefore Sotrovimab should not currently be used in San Francisco[1] and has been removed from this document.
- COVID-19 rebound is the recurrence of COVID-19 symptoms after recovery or a new positive viral test after having tested negative after initial diagnosis of COVID-19 in the past 2 weeks. It may be part of the natural history of SARS-CoV-2 infection in some persons, independent of treatment with Paxlovid and regardless of vaccination status. Limited information currently available from case reports suggests that persons treated with Paxlovid who experience COVID-19 rebound have had mild illness; there are no reports of severe disease. There is currently no evidence that additional treatment is needed with Paxlovid or other anti-SARS-CoV-2 therapies in cases where COVID-19 rebound is suspected (CDC Health Advisory May 24, 2022)

Table 1: Recommended COVID-19 Therapeutics for the outpatient setting

	Therapy	Mechanism & Administration	Clinical Considerations
1st Line	Nirmatrelvir/ Ritonavir (Paxlovid)	• Antiviral • **Oral:** Nirmatrelvir 300mg (two 150 mg tablets) with ritonavir 100mg (one 100mg tablet)- three tablets taken twice daily x 5 days within *5 days of symptom onset* • **Dose reduce for renal impairment**. For eGFR 30-60 ml/min- decrease dose to 150mg nirmatrelvir (one 150mg tablet) and 100mg ritonavir (one 100mg tablet) twice daily x 5 days. Formulations in renal dosing are available. Do not prescribe for eGFR <30 ml/min. • Do not use in severe hepatic impairment (ie Child-Pugh C, history of decompensated cirrhosis).	• Numerous drug interactions due to inhibitor of CYP3A4. Many interacting medications should be held or dose reduced for the 5 days of Paxlovid and 2 days after Paxlovid completion* • Limited data in pregnancy, but per EUA, should not be withheld in pregnancy • For use in individuals ≥12 years of age • May cause some GI symptoms • *Evidence:* 88% reduction in hospitalization and death[2]
	Remdesivir (Veklury)	• Antiviral • Intravenous: 200mg x1 day, then 100mg x 2 days within *7 days of symptom onset.* • Limited data in eGFR < 30 ml/min. Weigh risks and benefits. • Do not use in severe hepatic impairment ***Where available due to limitation of resources to offer it in outpt setting. Currently not available at any DPH outpatient facilities.***	• Limited drug interactions. Minor CYP3A4 inhibitor.* • Limited data in pregnancy but generally considered safe. • For use in individuals ≥12 years of age (per pediatric EUA, can also be used as outpatient treatment for pt <12 years of age weighing at least 3.5kg • *Evidence:* 87% reduction in hospitalization and death[3]
2nd Line	Molnupiravir **(Lagevrio)**	• Antiviral • **Oral**: 800mg (4 tablets of 200mg) twice daily for 5 days within *5 days of symptom onset.* • No adjustments for renal or hepatic insufficiency	• No drug interactions* • Contraindicated in pregnancy or while breastfeeding. Patients of childbearing potential should use contraception during and 4 days after use. Individuals with partners of childbearing potential should use contraception during and 3 months after use. • For use in individuals ≥**18 years of age** • May cause some GI symptoms • *Evidence:* 30% reduction in hospitalization and death[4]

	Bebtelovimab	• Monoclonal antibody with presumed activity against Omicron • **Intravenous**: 175mg x 1 dose *within 7 days of symptom onset.* • No adjustments for renal or hepatic insufficiency	• Drug interactions unlikely* • Limited data in pregnancy or during lactation but generally considered safe • For use in individuals ≥12 years of age weighing at least 40kg • Risk of an allergic reaction so should be monitored for 60 minutes after infusion • *Evidence:* Reduced time to symptom resolution. Data in low-risk individuals did not show reduction in hospitalization and death[5]

*Drug interactions for COVID-19 medications can be found here: https://www.covid19-druginteractions.org/

For Pre-exposure Prophylaxis: The following therapies in Table 2 can be considered for individuals who have moderate to severe immune compromise and may not be able to mount an adequate response to COVID-19 vaccination OR for whom vaccination is not recommended due to history of severe adverse reaction. See Table 2 for the mechanism of action, administration instructions, evidence for efficacy, and clinical considerations for each treatment.

Table 2: Recommended COVID-19 Therapeutics for Pre-exposure Prophylaxis

Therapy	**Mechanism & Administration**	**Clinical Considerations**
Tixagevimab/cilgavimab (Evusheld)	• Monoclonal antibody • **Intramuscular:** two IM injections of tixagevimab 300 mg and cilgavimab 300 mg • No adjustments for renal or hepatic insufficiency	• Drug interactions unlikely* • Limited data in pregnancy or during lactation. Should weigh risks and benefits. • For use in individuals ≥12 years of age weighing at least 40kg • Risk of an allergic reaction so should be monitored for 60 minutes after infusion. Should be used in caution in individuals with increased risk of bleeding or prior cardiovascular risk factors. In patients with bleeding disorders or on anticoagulation, optimization may include holding anticoagulants or infusing platelets • *Evidence:* 77% reduction in infection with COVID-19[6]

*Drug interactions for COVID-19 medications can be found here: https://www.covid19-druginteractions.org/

Prioritizing High-Risk Patients When There is Limited Supply of Therapeutics

The National Health Institute (NIH) has developed guidance on allocation of these therapies during times of low supply or high demand. In times of scarcity, COVID-19 therapies should be directed towards the patients who will have the greatest potential benefit based on vaccination status, age, and comorbidities (Table 3). This framework provides a guideline that individual health systems may choose to interpret differently to best serve their patients when supply is low or demand is high. Allocation of a scarce resource often poses equity concerns. The CDC released data that racial and ethnic minorities are less likely to receive certain outpatient treatments against COVID-19 which clinicians should consider in their practice 7.

The California Department of Public Health (CDPH) and SFDPH will be monitoring availability and prescribing practices and will adjust allocations and provider outreach as needed to enhance equitable access. Providers may choose to follow local and state Health Alerts to determine current availability and eligibility criteria for COVID-19 treatments. Health advisories and alerts are posted at www.sfcdcp.org/health-alerts-emergencies/health-alerts/.

Table 3: Risk Groups for COVID-19 Therapeutic Prioritization for Treatment of COVID-19

Tier 1	Tier 2	Tier 3***	Tier 4***
• Moderately or severely Immunocompromised patient not expected to have mounted response to the vaccine* • Unvaccinated individuals either 1) age >75; or 2) age >65 with clinical risk factors**	• Unvaccinated patients at risk of severe disease due to 1) age >65; or 2) age <65 with clinical risk factors**	• Vaccinated patients at high risk of severe disease due to 1) age >75; or 2) age >65 with clinical risk factors**	• Vaccinated patients at risk of severe disease due to 1) age >65; or 2) age <65 with clinical risk factors**

*Immunocompromising Conditions:

CDC lists conditions that qualify an individual as moderately or severely immunocompromised.

However, given supply may not reach all moderately to severely immunocompromised individuals, the following should be prioritized per NIH guidance:

- Patients within 1 year of receiving B-cell depleting therapies (rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Patients receiving tyrosine kinase inhibitors
- Chimeric antigen receptor T cell recipients
- Post-hematopoietic cell transplant recipients with chronic graft versus host disease or who are taking immunosuppressives
- Patients with hematologic malignancies on active therapy
- Most solid organ transplant recipients (see NIH guidance below for specifics)
- Patients with severe combined immunodeficiencies
- Patients with untreated HIV with CD4 counts <50

**Clinical risk factors can be found here: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

*** Vaccinated individuals who have not received the booster should be prioritized.

Pre-exposure prophylaxis priority groups per CDPH guidance

Pre-exposure prophylaxis should not be used for unvaccinated individuals unless they have a severe allergy to ingredients of the vaccine or a severe allergy to prior doses of the vaccine. Therapies used for pre-exposure should be allocated in the following priority groups.

- Priority 1: People who are severely immunocompromised by NIH treatment guidelines
- Priority 2: If adequate supply exists, then can be used for those who are moderately immunocompromised and not expected to mount an appropriate response.
- Priority 3: If adequate supply exists to meet the above demands, healthy people with no immunocompromising conditions but history of severe adverse reactions to the COVID-19 vaccine

Additional Resources

- NIH Guidance: "The COVID-19 Treatment Guidelines Panel's Statement on Therapies for High-Risk, Non-hospitalized Patients With Mild to Moderate COVID-19." https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-high-risk-nonhospitalized-patients/
- NIH Guidance: "The COVID-19 Treatment Guidelines Panel's Interim Statement on Patient Prioritization for Outpatient Anti-SARS-CoV-2 Therapies or Preventive Strategies When There Are Logistical or Supply Constraints" https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-patient-prioritization-for-outpatient-therapies/
- FDA's Paxlovid Eligibility Screening Checklist for Providers https://www.fda.gov/media/158165/download

References

1. Administration. FaD. Fact sheet for healthcare providers: emergency use authorization for Paxlovid. 2021. *Available at: https://www.fda.gov/media/155050/download.* 2021.
2. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab. *N Engl J Med.* 2021;385(21):1941-1950.
3. Gottlieb RL, Vaca CE, Paredes R, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. *N Engl J Med.* 2022;386(4):305-315.
4. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. *N Engl J Med.* 2021.
5. Administration. UFaD. Fact sheet for healthcare providers: Emergency Use Authorization for bebtelovimab. *Available at: https://www.fda.gov/media/156152/download.*
6. Administration. UFaD. FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR EVUSHELD (tixagevimab co-packaged with cilgavimab). *Available at: https://www.fda.gov/media/154701/download.*
7. Wiltz JL, Feehan AK, Molinari NM, et al. Racial and Ethnic Disparities in Receipt of Medications for Treatment of COVID-19 - United States, March 2020-August 2021. *MMWR Morb Mortal Wkly Rep.* 2022;71(3):96-102.