V.12 UCSF Adult Outpatient COVID-19 Treatment Guidance
Owner: UCSF Outpatient Treatment Guidance Task Force
7.17.23

Background: The Food and Drug Administration (FDA) has approved or provided Expanded Use Authorization (EUA) for several treatments for outpatients with mild-moderate COVID-19 who are at high risk for progression to severe infection. An EUA is a U.S. Food and Drug Administration authorization for the emergency use of an unapproved product or unapproved use of an approved product. In addition, recent data suggest benefit to outpatient administration of a short course of IV remdesivir to high-risk outpatients. This document contains information regarding how to prescribe these medications.

Table of changes:

Date	Change
1/5/22	Merged monoclonal antibody use document into this document to centralize material Clarified HSCT/CAR-T criteria Clarified timing of B-cell depleting agents Moved acute leukemia on active therapy to Group 1 Added contact information for transplant and OB teams Added information on outside pharmacies carrying oral agents
1/12/22	Added link to the therapeutic locator Added information about outpatient IV remdesivir treatment in the RSC for Group 1 patients as an alternative treatment when sotrovimab and nirmatrelvir-ritonavir are not available or options (go-live 1/18/22) Updated workflow for Specialty Pharmacy Removed screenshots for medications prescribed from Database Lookup
1/20/22	Corrected OB pool contact information Added requirement to document symptom onset timing for outside pharmacies Added NIH drug-drug interactions guidance link Updated HHS website with therapeutics availability Added UCSF Dashboard information
2/25/22	Expanded groups eligible for sotrovimab and nirmatrelvir/ritonavir Added links to Spanish translation of the EUAs Added link to CDC definition of fully vaccinated Added comment on management of patients with COVID-19 breakthrough infection after receipt of tixagevimab/cilgavimab for pre-exposure prophylaxis Updated CDC recommendations not to defer vaccination after receipt of mAb
4/3/22	Starting 4/4/22, UCSF Health will transition from sotrovimab to bebtelovimab due to increasing prevalence of the BA.2 Omicron variant With improved access to oral antivirals, we have removed the prior tiered groupings and organized treatments based on clinical evidence
5/11/22	Aligned definitions of high-risk individuals to CDC definitions Added information about requirements to adhere to the EUA
6/29/22	Added restriction for 3-day remdesivir treatment to highest-risk patients Specified age considered to be high risk for progression Corrected current name of REF778 and updated screenshots Corrected broken link Removed Appendix A and replaced with reference to the EUA
11/16/22	Removed bebtelovimab as a treatment option due to increased circulating variants resistant to this antibody
2/6/23	Updated inclusion criteria to reflect recent changes in FDA guidance on requirement for positive test Changed criteria for remdesivir during non-surge times

7/17/23	Updated guidance to reflect FDA approval of nirmatrelvir-ritonavir in adults (nirmatrelvir-ritonavir is still under FDA EUA for pediatric patients ≥ 12 yo and weighing at least 40 kg) Updated information about how to order outpatient remdesivir

Stepwise approach:

1. Evaluate eligibility for outpatient therapeutics

Inclusion criteria: Meets all of these and no Exclusions*
Symptomatic with symptom onset within time frames outlined below
Mild-moderate disease (see Definitions)
Meets at least one of high-risk for progression to severe COVID-19 criteria (see CDC website)

*Nirmatrelvir/ritonavir (Paxlovid) and molnupiravir (Lagevrio) may both be prescribed without documentation of a positive test but should only be *used* in patients with current diagnosis of mild-to-moderate COVID-19, ideally with SARS-2-CoV viral tests confirmation or documented high-risk household exposure

Exclusion criteria
Hospitalized *for* COVID-19^
New O2 requirement
Worsening O2 requirement in those on supplemental O2

^If the patient is hospitalized for another indication, you can consider these therapies. Consult with Infectious Diseases or Antibiotic Stewardship to discuss

High-risk for progression to severe COVID-19

- See: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html
- Age>50, with risk increasing with older age

Illness severity

- Mild: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging and who do not meet criteria for moderate, severe, or critical illness
- Moderate: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging, and a saturation of oxygen (SpO2) ≥94% on room air at sea level.

- For molnupiravir, prescribers must adhere to the Emergency Use Authorization. The medication is not approved by the FDA and should not be prescribed outside of the specifications of the EUA.
- Nirmatrelvir/ritonavir is not approved for use as a pre-exposure or post-exposure prophylaxis for prevention of COVID-19

If patient meets the above criteria→move onto step 2

If patient does not meet above criteria→STOP here; not currently eligible for outpatient treatment

2. Evaluate time since symptom onset

- Treatment with antivirals is likely to be more effective earlier in the course of illness
- Nirmatrelvir/ritonavir was authorized under the EUA for patients within 5 days of symptom onset based on how it was studied. Now that it is FDA approved, there is more flexibility in administration. In general, prescribers should follow institutional and national (NIH) guidance. Consult with ID if there are questions about off-label use.
- Remdesivir was studied in outpatients within 7 days of symptom onset. Now that it is FDA approved, there is more flexibility in administration. In general, prescribers should follow institutional and national (NIH) guidance. Consult with ID if there are questions about off-label use.
- Molnupiravir is still under EUA and should only be administered if within 5 days of symptom onset.

3. Evaluate treatment recommendation

- Do not give more than one drug to an individual patient given lack of data for this approach
- Use first-line agents preferentially if able (see below). If limited supplies or contraindications, use second-line agent

	Recommendation
First line	**Nirmatrelvir/ritonavir (Paxlovid)**
	IV remdesivir x 3 days[#]
Second line*	**Molnupiravir (Legevrio)**

[#]During periods of surge where demand exceeds capacity for IV therapy, remdesivir will be restricted to the following high-risk populations (see https://www.covid19treatmentguidelines.nih.gov/overview/prioritization-of-therapeutics/):

- Immunocompromised individuals not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying conditions, regardless of vaccine status (see below); *or*
- Unvaccinated individuals at the highest risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with additional risk factors)

*Second-line therapies should be used when preferred treatments are not available, contraindicated, or not feasible to use

Immunocompromised host/Not expected to mount an adequate immune response to complete vaccination

- Active treatment for solid tumor and hematologic malignancies
- Hematologic malignancies associated with poor responses to COVID-19 vaccines regardless of current treatment status (e.g., chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, acute leukemia)
- Receipt of solid-organ transplant and taking immunosuppressive therapy
- Receipt of CAR T-cell or HSCT (within 2 years of transplantation or taking immunosuppressive therapy)
- Moderate or severe primary immunodeficiency (e.g., DiGeorge, Wiskott-Aldrich syndromes)
- Advanced or untreated HIV infection
- Active treatment with high-dose corticosteroids or other drugs that may suppress your immune response
- Other diagnosed chronic condition with severe level of immunocompromise.

4. Evaluate for contraindications and cautions

	Nirmatrelvir/ritonavir (Paxlovid)	3-day remdesivir	Molnupiravir (Lagevrio)
Standard Dose	Nirmatrelvir 300mg (two 150 mg tablets) with 100 mg ritonavir (one 100mg tablet), with all three tablets taken together twice daily for 5 days with or without food	200 mg IV on day 1 followed by 100 mg IV qday on days 2 and 3	800mg (4 tablets) orally every 12 hours x 5 days with or without food
Drug-Drug Interactions	-Substrate and inhibitor of CYP3A4. -Review Table 1 of the drug Package Insert and The Liverpool COVID-19 Drug Interaction Checker -NIH guidelines here -Must discuss management of immunosuppression with Transplant team before prescribing*	Minor CYP3A4 substrate; inducers may ↓levels. Dose adjustment not required	None
Fertility/Pregnancy/ Lactation	-Limited data. Discuss with OB (MFM) and Pediatrics on a case-by-case basis (weekdays: send an Apex staff message to "P OBGYN COVID". Overnight/urgent messages: contact the MFM on-call on Voalte)	-Limited data, generally considered safe -Discuss with OB (MFM) on a case-by-case basis (weekdays: send an Apex staff message to "P OBGYN COVID". Overnight/urgent messages: contact the MFM on-call on Voalte)	-Use not recommended -Prior to treatment, assess whether an individual of childbearing potential is pregnant if indicated -Nursing individuals should pump and discard milk during and for 4 days after last dose
Contraception Considerations	-Ritonavir may reduce effectiveness of hormonal contraceptives. Use alternative method while taking Paxlovid	None	-Patients with childbearing potential should use effective contraception during and for 4 days after the last dose -Individuals with partners of childbearing potential should use

	Nirmatrelvir/ritonavir (Paxlovid)	3-day remdesivir	Molnupiravir (Lagevrio)
			contraception during treatment and for 3 months after last dose
Renal Insufficiency	-For eGFR ≥ 30 ml/min and ≤ 60 ml/min: decrease dose to 150 mg nirmatrelvir (one 150 mg tablet) and 100 mg ritonavir (one 100 mg tablet) twice daily x 5 days with or without food -Not recommended for eGFR < 30 ml/min	Contains cyclodextrin, which can accumulate in renal disease; clinical significance of accumulation is uncertain. Limited data in eGFR<30, and short durations may be safe	No adjustment
Hepatic Insufficiency	Not recommended in severe hepatic impairment	Not recommended in severe hepatic impairment	No adjustment
Comments			

***Transplant contacts for urgent questions:**

Service	Daytime contact	After-hours contact
Lung transplant	Leslie Seijo MD (Voalte)	Pager: (415) 443-8258
Heart transplant	AHF/ Transplant fellow on call (on amion)	AHF/Transplant fellow on call (on amion)
Liver transplant	Call statline to reach assigned APP: 415-353-1888	Surgeon on call (on amion)
Kidney/pancreas transplant	KTU inpatient attending (check on amion)	KTU inpatient fellow/ attending (check on amion)
HSCT	Mimi Lo, PharmD (text work cell 415-806-5166 OR Voalte). Back-up: 415-353-2920	Malig Hematology FELLOW Pager 415.443.2180

Transplant pharmacy contacts:

Voalte:
9 KTU1 or 9KTU2 for kidney/pancreas transplant pharmacist
9 LTU for liver transplant pharmacist
10 Heart & Lung transplant pharmacist

Telephone:
Heart transplant: 353-8803
Lung transplant: 353-8803
Liver transplant: 353-1462
Kidney/pancreas transplant: 353-1335

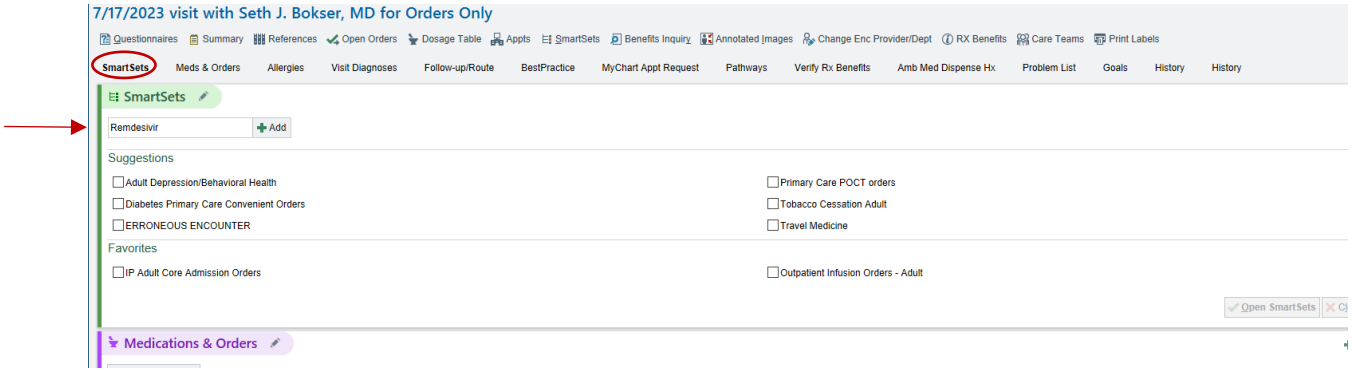
5. Discuss potential risks, benefits, and alternatives with the patient and provide the patient with the EUA fact sheet (for molnupiravir)

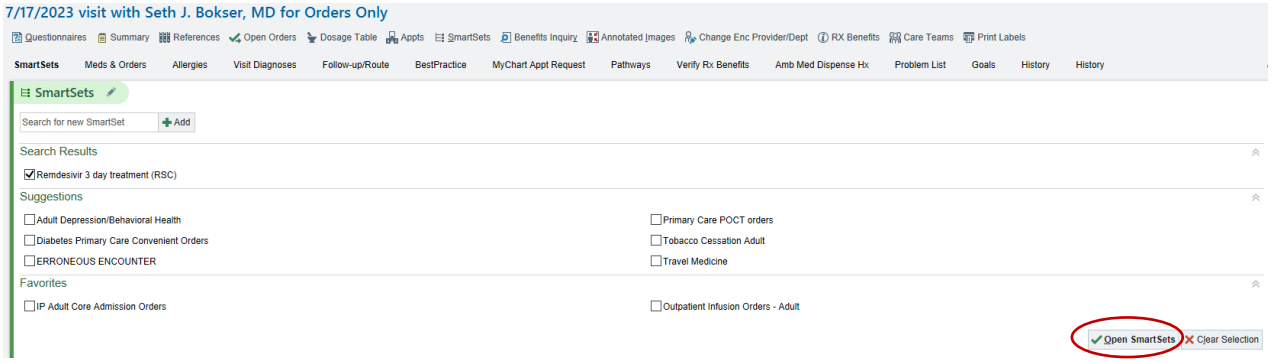
- Molnupiravir (Lagevrio): English and Spanish

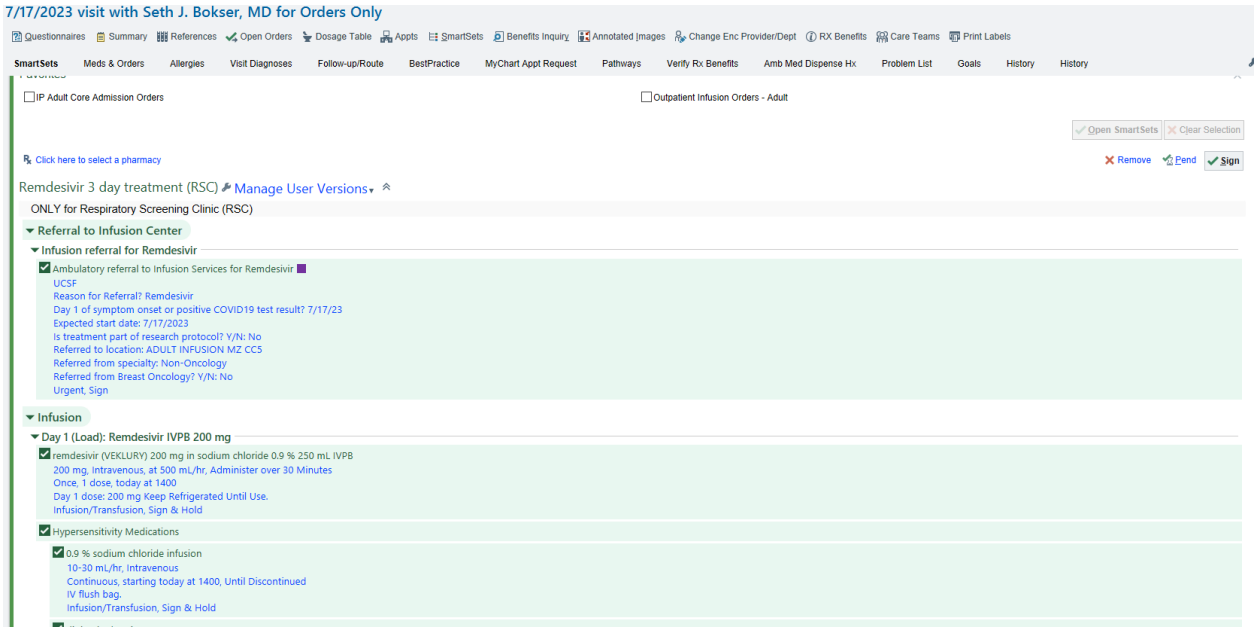
6. Prescribe medication:

Information about Test-to-Treat locations and other pharmacies: https://covid-19-test-to-treat-locator-dhhs.hub.arcgis.com/

- **Short-course IV remdesivir:**
  - Outpatient providers may now order remdesivir to be given at the Mt. Zion Infusion Center directly for eligible patients
  - Order via SMARTSET (see screenshots below)
    - The ordering clinician must order both the medication and place the referral. Both of these orders are included in the smartest
    - Search for "remdesivir"→Open Smartset→complete embedded questions→sign orders→sign encounter







- **Nirmatrelvir/ritonavir or molnupiravir:**
    - Start an encounter with capability for order placement
    - Write prescription
        - Find the medication on your Preference List or Facility List, select correct dosage for renal function
            - Answer order questions and select “Accept”
        - Sign order

<u>Reviewed by representation from:</u>

- Respiratory Screening Clinic
- Emergency Department
- Infectious Diseases
- Medical specialties
- Care Delivery
- Nursing
- Pharmacy
- Ethics

References:

Bernal AJ, et al. NEJM 2021: DOI: 10.1056/NEJMoa2116044

Gottlieb RL, et al. NEJM 2021: DOI: 10.1056/NEJMoa2116846

Gupta A, et al. NEJM 2021: DOI: 10.1056/NEJMoa2107934

Hammond J, et al. NEJM 2022: DOI: 10.1056/NEJMoa2118542

Molnupiravir Fact Sheet for Healthcare Providers

Paxlovid Fact Sheet for Healthcare Providers (for pediatric patients ≥12 yo and ≥ 40 kg)

Paxlovid Package Insert (for adults)