V.5 UCSF Health Guidance for Adult COVID-19 Pre-Exposure Prophylaxis (passive immunity)
Author: Adult COVID-19 Monoclonal Antibody Use Task Force
1.25.2022

Background: On December 8, 2021, the U.S. Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for tixagevimab and cilgavimab (Evusheld, AztraZeneca) for use as pre-exposure prophylaxis (prevention) of COVID-19 in certain eligible patients who are not currently infected nor exposed to COVID-19. This drug is not a substitute for vaccination, and all patients who can receive vaccination should do so. This document contains information about how the drug will be allocated to adults at UCSF Health.

For treatment of COVID-19 infection with monoclonal antibodies, refer to the UCSF Adult Monoclonal Antibody Use Process for Treatment here.

Table of changes:

1/7/22	Updated booster timing consistent with CDC guidelines Added definition of maximally vaccinated for newly immunosuppressed patients Clarified that patients with very recent transplants can receive Evusheld regardless of whether maximally vaccinated and regardless of spike positivity pre-transplant Added information about timing of vaccine post-tixagevimab/cilgavimab infusion
1/12/22	Removed requirement for spike Ab to be checked before referral Added factors to consider when determining which patients to refer for treatment Updated plan for inpatient administration
1/25/22	Updated EUA fact sheet link and added Spanish EUA link Clarified that outpatients will be scheduled for visits with authorization pending Added Appendix "Clinical considerations for pre-exposure prophylaxis referral prioritization"

Definitions:

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

- Active treatment for solid tumor and hematologic malignancies
- 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.

Maximally vaccinated. This means completion of the following:

- **mRNA**: At minimum, 3 doses required (for initial series, 3 full doses preferred; 2 full doses plus 1 booster dose acceptable)
  - If <5 months since dose #3, the patient is considered maximally vaccinated
  - If >5 months since dose #3, the pt is eligible for and must receive dose #4/booster to be considered maximally vaccinated
- For newly immunosuppressed patients who received vaccination prior to becoming immunosuppressed (i.e. new SOT, HSCT, CAR-T treatment), maximally vaccinated includes 2 mRNA doses and a third booster dose 5 months later (if eligible by timing)
- **J+J**: Initial shot followed by booster (mRNA preferred) 2 months later
- For details: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html?s_cid=10483:immunocompromised%20covid%20vaccine:sem.ga:p:RG:GM:gen:PTN:FY21

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Eligibility for Monoclonal Antibodies for Pre-Exposure Prophylaxis (PrEP) of COVID-19 via EUA for immunocompromised hosts:

1. Adult patient ≥ 18 years old
2. Weight ≥ 40 kg
3. Meets definition of Immunocompromised host/Not expected to mount an adequate immune response to complete vaccination (see Definitions)
4. Maximally vaccinated (see Definitions)^
5. Not currently symptomatic or known to be infected with COVID-19
6. No recent COVID-19 close contact exposures (https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html)
7. Not allergic to any component of tixagevimab/cilgavimab (Evusheld) injection
8. Has not received COVID-directed mAb therapy within prior 90 days that has predicted activity against current circulating strains

^For patients within 90 days of transplant (SOT or HSCT) or CAR-T cell therapy, tixagevimab/cilgavimab may be administered even if does not yet meet maximal vaccination criteria

Eligibility for Monoclonal Antibodies for Pre-Exposure Prophylaxis (PrEP) of COVID-19 via EUA for patients with medical vaccine contraindication:

1. Adult patient ≥ 18 years old
2. Weight ≥ 40 kg
3. Maximal vaccination is medically contraindicated due to history of severe adverse reaction to vaccines
4. Not currently symptomatic or known to be infected with COVID-19
5. No recent COVID-19 close contact exposures (https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html)
6. Not allergic to any component of tixagevimab/cilgavimab (Evusheld) injection
7. Has not received COVID-directed mAb therapy within prior 90 days that has predicted activity against current circulating strains

Dosing:

-150 mg tixagevimab and 150 mg cilgavimib administered as two separate IM injections (gluteal)
-May be redosed every 6 months if patient still meets the criteria above

General guidance for those at risk of bleeding:

Proceed with caution in these populations
Thrombocytopenia with platelets < 30 (Patient to receive platelets the morning of each dose of injection and apply manual pressure to injection site for 10 minutes following injection)
Severe bleeding diathesis (Must not have supratherapeutic INR if on warfarin; discuss as needed with patient's Hematologist or Hematology e-consultant)

- All lab orders will be placed by the referring clinician.
- If an intervention is recommended, please discuss directly with your patient, and include information in the or "OK to treat" section of the PrEP Therapy Plan
- All: Hold pressure x10 min (sit) post injection and monitor for hematoma formation
- IM Vaccination in Adults with Therapeutic Anticoagulation Article

Platelets

- If no concern for thrombocytopenia, ok to inject drug
- If patient is at risk for thrombocytopenia
    - OK to inject mAb if platelet count >30k checked in the past 30 days
      OR
    - Concern that platelet count may be <30K; check CBC the same day pre-IM injection; If plt <30K, transfuse 1 unit of platelets in the Parnassus infusion center (PIC) and inject during or after; confirmatory count not needed. Contact Shagun Arora if this is needed.

On vitamin K antagonist/coumadin

- Platelet as above and
- If well controlled INR and no concern for supratherapeutic INR, ok to inject mAb without checking INR.
- If concern for uncontrolled INR, check INR same day as injection
    - If INR <4 ok to inject
    - If INR ≥4, injection will be rescheduled and referred back to referring clinician.

On direct-acting anticoagulant (DOAC) /low molecular weight heparin (LMWH)

- Platelet as above and
- If no concern for bleeding, ok to inject mAb
  OR
- Advise patient to hold DOAC or LMWH dose for 24 hours before IM injection (ie last dose morning prior to the IM Injection) and resume the same day evening or next day morning.

Severe hemophilia – most patients are on prophylactic factor replacement

- Platelet as above and
- Advise patient to self-administer factor replacement on the morning scheduled for IM mAb injection
- Hold pressure x10min post injection and monitor for hematoma formation

Timing of tixagevimab/cilgavimab (Evusheld) and COVID-19 vaccination

It is not known whether monoclonal antibodies for COVID-19 prevention interfere with vaccine response, though the theoretical concern has been raised. When possible, patients should receive COVID-19 vaccination at least 2 weeks prior to tixagevimab/cilgavimab administration. The CDC

recommends deferring vaccine for 90 days after monoclonal antibody administration for COVID-19 infection and 30 days after administration for *post*-exposure prophylaxis but has not provided recommendation for *pre*-exposure prophylaxis. One case report looking at antibody response after bamlanivimab treatment for COVID-19 infection demonstrated serological response comparable to that of patients who did not receive antibody treatment when vaccine was started 20 days after antibody receipt. Tixagevimab/cilgavimab (Evusheld) has a longer half-life than all other monoclonal antibodies and the optimal timing between tixagevimab/cilgavimab and subsequent vaccination is unknown.

Balancing the theoretical risk for interference with vaccine response and importance of continuing with recommended schedules of booster doses, vaccine can be administered starting 30 days after tixagevimab/cilgavimab (Evusheld).

Allocation:

Guiding principles

- No patient should be denied access to pre-exposure prophylaxis based on age, disability, religion, race, ethnicity, national origin, immigration status, gender/gender identity, perceived quality of life, or sexual orientation
- To maximize distribution of drug, the medication should not be stockpiled for future use
- Patients eligible for pre-exposure prophylaxis via clinical trials should be offered participation in the trials but should not be compelled to participate in trials for the sole purpose of accessing the drug. Patients who opt not to participate in trials shall be offered pre-exposure prophylaxis via the EUA if eligible.

Process

Among individuals eligible for receipt of the agent by the guidelines above, allocation will occur as outlined in the detailed Tixagevimab/cilgavimab (Evusheld) Allocation Guidance document when drug supply is limited. Patients referred for treatment may not receive treatment right away in the setting of demand outstripping supply.

Inpatient PrEP Workflow

Starting 1/18/22, PrEP may be administered to eligible inpatients meeting criteria.

Primary provider should:

1. Discuss potential risks, benefits, and alternatives with the patient
2. Provide patient/caregiver with EUA fact sheet (English or Spanish)

Outpatient PrEP Workflow (see screenshots below)

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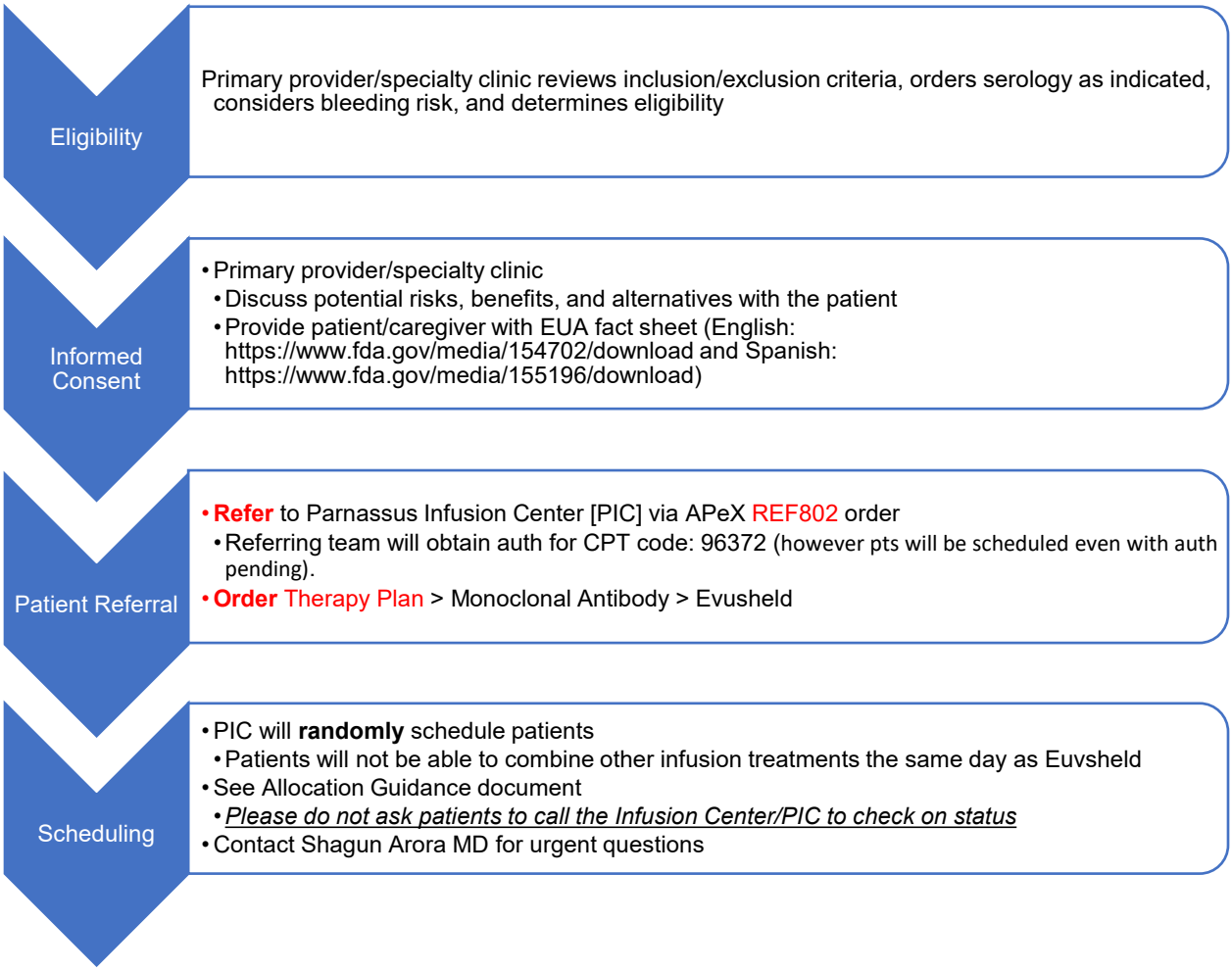

EUVSHELD – how to REFER and ORDER therapy plan

REFERRAL REF802:

1. Open an encounter where orders can be placed.

2. Enter REF802 in the Order Search Bar at the bottom of your screen

3. Review Scheduling instructions

4. Enter comments if needed

5. Sign order.

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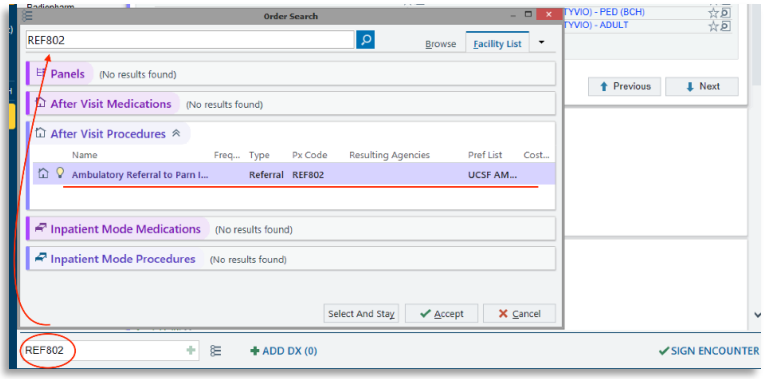
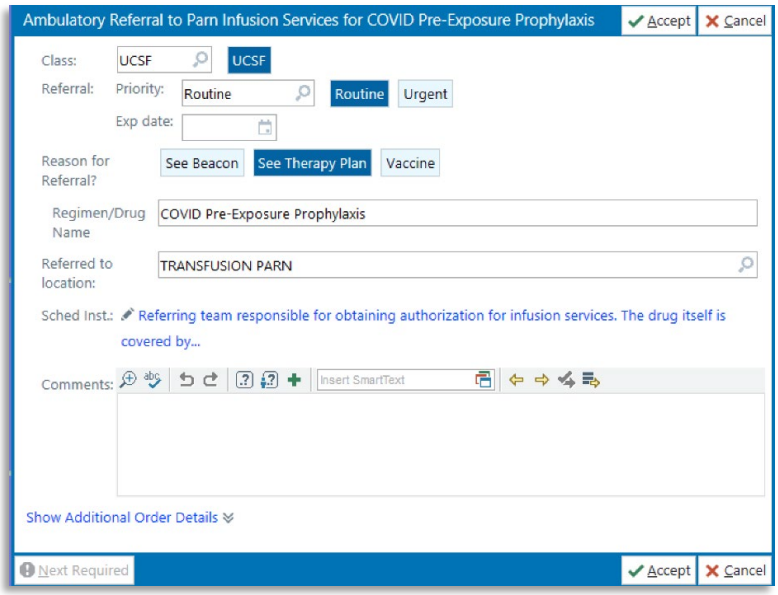


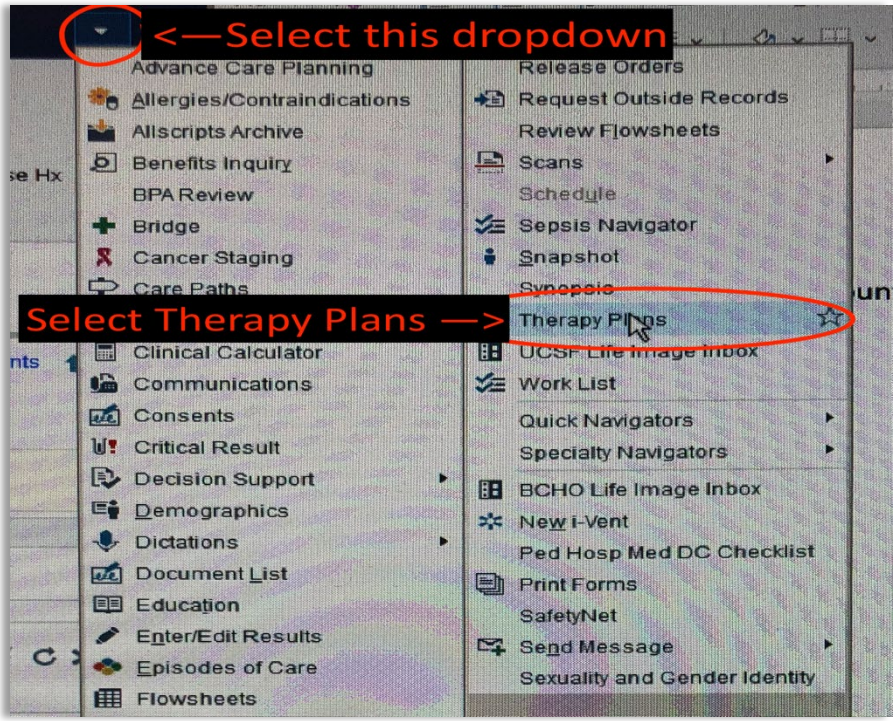


THERAPY PLAN

1. Open an **Orders Only Encounter**

2. Click on the **Dropdown Arrow** at the TOP RIGHT of you screen (just to the left of the wrench)

3. Select **Therapy Plans**



4. Select **Monoclonal Antibodies** on the Left.

5. Select **AMB EVUSHELD** (or enter EVUSHELD into the search field)

6. Complete and Sign therapy plan, Sign encounter.

Appendix A: Clinical considerations for pre-exposure prophylaxis referral prioritization

There is no well-validated scoring system to predict risk of COVID infection and/or severe outcomes in immunocompromised patients. In addition, data supporting the use of pre-exposure prophylaxis in immunocompromised patients is limited. Each clinic caring for patients with moderate to severe immunocompromise will develop a systematic approach to ordering of pre-exposure prophylaxis for their patients that provides an equitable and rational approach to evaluating potential benefit from this treatment. The approach may vary between clinics given different underlying medical conditions and other considerations.

Factors to consider in determining which patients may benefit the most from this treatment may include all or some of the following:

- Biomarkers for vaccine response, such as undetectable or low SARS-CoV-2 spike antibody
- Level of immunosuppression as reflected by the institutional tiered system (see below). Other factors, such as time from transplant, if applicable, and need for augmented immunosuppression, can also be considered:

    1. Tier One Immunocompromised Hosts:
        - Treatment with B-cell depleting therapy within one year (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab)
        - HSCT / CAR-T within 2 years of transplant, or on immunosuppressive medications
        - Multiple myeloma on therapy
        - CLL on therapy
        - Acute leukemia on therapy
        - Solid organ transplant and on immunosuppressive medications
        - Severe congenital immunodeficiency
    2. Tier Two Immunocompromised Hosts:
        - Other hematological malignancy on active treatment
        - Other immunosuppressive conditions on active immunosuppressive therapy
        - CVID
        - Advanced or untreated HIV infection
- Advanced age
- Number of medical comorbidities
- Exposure risk based on occupation or living arrangement
- Measures of social vulnerability, such as the Social Vulnerability Index or the California Healthy Places Index
- Other clinician-determined medical or demographic factors presumed to place the patient at high risk for COVID-19 exposure or severe disease