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:

<table>
<thead>
<tr>
<th>Date</th>
<th>Changes</th>
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</thead>
<tbody>
<tr>
<td>1/7/22</td>
<td>Updated booster timing consistent with CDC guidelines&lt;br&gt;Added definition of maximally vaccinated for newly immunosuppressed patients&lt;br&gt;Clarified that patients with very recent transplants can receive Evusheld regardless of whether maximally vaccinated and regardless of spike positivity pre-transplant&lt;br&gt;Added information about timing of vaccine post-tixagevimab/cilgavimab infusion</td>
</tr>
<tr>
<td>1/12/22</td>
<td>Removed requirement for spike Ab to be checked before referral&lt;br&gt;Added factors to consider when determining which patients to refer for treatment&lt;br&gt;Updated plan for inpatient administration</td>
</tr>
<tr>
<td>1/25/22</td>
<td>Updated EUA fact sheet link and added Spanish EUA link&lt;br&gt;Clarified that outpatients will be scheduled for visits with authorization pending&lt;br&gt;Added Appendix “Clinical considerations for pre-exposure prophylaxis referral prioritization”</td>
</tr>
<tr>
<td>2/22/22</td>
<td>Removed requirement for weight &gt;40 kg for adults (this limit only applies to pediatrics)&lt;br&gt;Updated definitions of maximal vaccination to reflect updated CDC guidance&lt;br&gt;Updated recommendations about timing of vaccine after mAb administration</td>
</tr>
<tr>
<td>3/16/22</td>
<td>Updated dosing to reflect latest FDA guidance&lt;br&gt;Added section on how to order catch-up dosing</td>
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<tr>
<td>4/3/22</td>
<td>Removed requirement for maximal vaccination; unless there is a medical contraindication, must be seeking to complete vaccination series&lt;br&gt;Updated guidance on catch-up dosing to reflect new FDA guidance based on time since prior dose</td>
</tr>
<tr>
<td>4/19/22</td>
<td>Updated CPT code</td>
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Definitions:

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

1. Adult patient ≥ 18 years old
2. Meets definition of Immunocompromised host/Not expected to mount an adequate immune response to complete vaccination (see Definitions)
3. Must be in the process of becoming up-to-date with COVID-19 vaccination, including primary series plus booster shots, as outlined by the CDC
4. Not currently symptomatic or known to be infected with COVID-19
6. Not allergic to any component of tixagevimab/cilgavimab (Evusheld) injection
7. Has not received COVID-directed mAb therapy (e.g., bebtelovimab) within prior 90 days.

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. Up-to-date vaccination is medically contraindicated due to history of severe adverse reaction to vaccines
3. Not currently symptomatic or known to be infected with COVID-19
5. Not allergic to any component of tixagevimab/cilgavimab (Evusheld) injection
6. Has not received COVID-directed mAb therapy (e.g., bebtelovimab) within prior 90 days.

**Dosing:**

- 300 mg tixagevimab and 300 mg cilgavimab administered as two separate IM injections (gluteal)
- For patients who received the prior 150 mg dosing of tixagevimab/cilgavimab, a catch-up dose may be administered:
If the patient received their initial dose ≤ 3 months ago, the patient should receive a dose of 150 mg of tixagevimab and 150 mg of cilgavimab.

If the patient received their initial dose > 3 months ago, the patient should receive a dose of 300 mg of tixagevimab and 300 mg of cilgavimab.

Redosing guidance is forthcoming.

**General guidance for those at risk of bleeding:**

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

- 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.
- 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.
  - 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**

Tixagevimab/cilgavimab should be delayed two weeks after latest vaccine dose. However, according to the [CDC](https://www.cdc.gov), COVID-19 vaccination does not need to be delayed after mAb administration.

**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](https://example.com) or [Spanish](https://example.com))
Outpatient PrEP Workflow for New Starts (see screenshots below)

Eligibility

Primary provider/specialty clinic reviews inclusion/exclusion criteria, orders serology as indicated, considers bleeding risk, and determines eligibility

Informed Consent

• Primary provider/specialty clinic
• Discuss potential risks, benefits, and alternatives with the patient
• Provide patient/caregiver with EUA fact sheet (English: https://www.fda.gov/media/154702/download and Spanish: https://www.fda.gov/media/155196/download)

Patient Referral

• Refer to Parnassus Infusion Center [PIC] via APeX REF802 order
• Referring team will obtain auth for CPT code: CPT-M0220 (however pts will be scheduled even with auth pending).
• Order Therapy Plan > Monoclonal Antibody > Evusheld New Start

Scheduling

• Injection clinics will randomly schedule patients
• Patients will not be able to combine other infusion treatments the same day as Euvsheld
• See Allocation Guidance document
• Please do not ask patients to call the Infusion Center/PIC to check on status
• Contact Shagun Arora MD for urgent questions

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.
THERAPY PLAN

1. Open an Orders Only Encounter

2. Click on the Dropdown Arrow at the TOP RIGHT of your 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.
Catch-up dosing

On 2/24/22, the FDA revised the emergency use authorization for tixagevimab/cilgavimab (Evusheld) to recommend a higher dose (300 mg tixagevimab and 300 mg cilgavimab) due to data suggesting better activity against circulating Omicron variants with this dosing approach. As part of this revision, the FDA recommends that patients who previously received the drug at the prior lower dose (150 mg tixagevimab and 150 mg cilgavimab), return to receive a catch-up dose of an additional 150 mg of tixagevimab and 150 mg of cilgavimab. Due to the dosing change, updated orders must be placed for individuals who have previously received or are in the work queue to receive tixagevimab/cilgavimab (Evusheld) but have the lower dose ordered.

On 4/1/22, the FDA further revised the recommendation for the catch-up dose based on time since receipt of the initial dose:

- If the patient received their initial dose ≤ 3 months ago, the patient should receive a dose of 150 mg of tixagevimab and 150 mg of cilgavimab
- If the patient received their initial dose > 3 months ago, the patient should receive a dose of 300 mg of tixagevimab and 300 mg of cilgavimab.

Here are the steps that must be taken for patients who received tixagevimab/cilgavimab (Evusheld) or had or had orders placed for tixagevimab/cilgavimab (Evusheld) before the dose change:

1. For patients who have already received an initial dose of 150 mg tixagevimab/cilgavimab (Evusheld) in the Parnassus Infusion Center at UCSF and need a catch-up dose:
   a. Contact your patient(s) via MyChart and/or telephone to alert them to the recommendation for a supplemental dose and to set expectations that they will receive a call to schedule this catch-up dosing, which will take place at Laurel Heights.
   b. Order catch-up dose:
      i. <3 months since initial dose: Edit the Therapy Plan using the Tip Sheet for Evusheld Catch-up Dosing.
      ii. ≥3 months since the initial dose: Delete the existing Therapy Plan and reorder the updated New Start Therapy Plan for 300 mg of tixagevimab and 300 mg of cilgavimab by following the Tip Sheet for Evusheld Increased Dose.
   c. The Population Health scheduling team will automatically contact your patients to schedule the catch-up dose.

2. For patients who have already received an initial dose of 150 mg of tixagevimab/cilgavimab (Evusheld) in the inpatient setting or at a facility outside of UCSF Health:
   a. Contact your patient(s) via MyChart and/or telephone to alert them to the recommendation for a supplemental dose and to set expectations that they will receive a call to schedule this catch-up dosing, which will take place at Laurel Heights.
   b. Order catch-up dose:
V.9 UCSF Health Guidance for Adult COVID-19 Pre-Exposure Prophylaxis (passive immunity)
Author: Adult COVID-19 Monoclonal Antibody Use Task Force
4.19.2022

i.  <3 months since initial dose: Order Therapy Plan > Monoclonal Antibody > Evusheld Second (Catch-Up) Dose

ii. ≥3 months since the initial dose: Order Therapy Plan > Monoclonal Antibody > Evusheld New Start

c.  Refer to Parnassus Infusion Center [PIC] via APeX REF802 order

   1.  Referring team must obtain auth for CPT code: M0220 (however pts will be scheduled even with auth pending).

3.  For **patients who have not yet received tixagevimab/cilgavimab (Evusheld) but who have active Therapy Plans** for the 150 mg dosing and **are scheduled or in the work queue for scheduling** (ie REF802 was placed):

   a.  Delete the existing Therapy Plan and reorder the updated New Start Therapy Plan for 300 mg of tixagevimab and 300 mg of cilgavimab by following the Tip Sheet for Evusheld Increased Dose.

4.  For **patients who do not yet have active Therapy Plans** (ie you have not placed REF802 nor Evusheld therapy plan), the tixagevimab/cilgavimab (Evusheld) Therapy Plan New Start Order now contains the appropriate dosing (300 mg of tixagevimab and 300 mg of cilgavimab) for newly placed therapy plan orders, so will not require additional steps moving forward. See “Outpatient PrEP Workflow for New Starts”
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