

The COVID-19 Treatment Guidelines Panel's Statement on Tixagevimab Plus Cilgavimab (Evusheld) for Pre-Exposure Prophylaxis for SARS-CoV-2 Infection

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Vaccination remains the most effective way to prevent SARS-CoV-2 infection, and it should be considered the first line of prevention. However, some individuals cannot or may not mount an adequate immune response to COVID-19 vaccines. Others may not have been fully vaccinated because of documented adverse reactions to the available vaccines or their components.

Based on the results of PROVENT, a large randomized controlled trial (ClinicalTrials.gov Identifier [NCT04625725](https://clinicaltrials.gov/ct2/show/study/NCT04625725)), the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) on December 8, 2021, for the anti-SARS-CoV-2 monoclonal antibodies (mAbs) tixagevimab plus cilgavimab (Evusheld).¹ The EUA allows this combination to be used as pre-exposure prophylaxis (PrEP) in certain individuals who, if infected, are at high risk of progressing to severe COVID-19. These mAbs are SARS-CoV-2 spike protein-directed attachment inhibitors that bind to nonoverlapping regions of the receptor binding domain of the SARS-CoV-2 spike protein. A modification in the Fc region gives these anti-SARS-CoV-2 mAbs prolonged half-lives; as a result, they may be able to protect a recipient from SARS-CoV-2 infection for up to 6 months. This combination of mAbs appears to have activity against the B.1.617.2 (Delta) variant. Although preliminary in vitro data suggest that the B.1.1.529 (Omicron) variant remains susceptible to this combination, more data are needed to fully assess the activity of this regimen in situations where the Omicron variant is circulating at high levels.¹⁻³

Recommendations

The COVID-19 Treatment Guidelines Panel recommends using **tixagevimab plus cilgavimab** as SARS-CoV-2 PrEP for adults and adolescents (aged ≥ 12 years and weighing ≥ 40 kg) who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection, **AND** who:

- Are moderately to severely immunocompromised and may have an inadequate immune response to COVID-19 vaccination (**BIIa**); *or*
- Are not able to be fully vaccinated with any available COVID-19 vaccines due to a documented history of severe adverse reactions to a COVID-19 vaccine or any of its components (**AIIa**).

If supplies of tixagevimab plus cilgavimab are limited, priority should be given to those who are at the highest risk for severe COVID-19 (see the Panel's statement on [prioritizing patients for outpatient therapies when there are logistical or supply constraints](#)).

Tixagevimab plus cilgavimab is not a substitute for COVID-19 vaccination and should not be used in unvaccinated individuals for whom COVID-19 vaccination is recommended and who are anticipated to have an adequate response.

The individuals who qualify as having moderate to severe immunocompromising conditions under this EUA are those who:

- Are receiving active treatment for solid tumors and hematologic malignancies.
- Received a solid organ transplant and are taking immunosuppressive therapy.
- Received a chimeric antigen receptor T cell therapy or a hematopoietic stem cell transplant (within

2 years of transplantation or taking immunosuppression therapy).

- Have a moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome).
- Have advanced or untreated HIV infection (defined as people with HIV and CD4 T lymphocyte cell counts $<200/\text{mm}^3$, a history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV).
- Are receiving active treatment with high-dose corticosteroids (i.e., ≥ 20 mg prednisone or equivalent per day administered for ≥ 2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents that are classified as severely immunosuppressive, tumor-necrosis blockers, and other biologic agents that are immunosuppressive or immunomodulatory (e.g., B cell-depleting agents).

Additional Information

- Each package of Evusheld includes a vial of tixagevimab and a vial of cilgavimab, each containing a single 150 mg/1.5 mL dose (100 mg/mL concentration per vial). These doses are administered as 2 consecutive intramuscular (IM) injections.
- People who continue to meet the criteria for the use of tixagevimab plus cilgavimab for PrEP and who remain in a setting with ongoing SARS-CoV-2 circulation can be redosed every 6 months.
- If a person has received a COVID-19 vaccine, tixagevimab plus cilgavimab should be administered ≥ 2 weeks after vaccination.

Clinical Trial Data

PROVENT is an ongoing, double-blind, Phase 3 randomized controlled trial that evaluated the use of tixagevimab plus cilgavimab for SARS-CoV-2 PrEP. The study enrolled adults aged ≥ 18 years who had not received a COVID-19 vaccine and who were at increased risk of severe SARS-CoV-2 infection (e.g., those aged ≥ 60 years, those who had a prespecified comorbidity) or who had an increased risk of acquiring SARS-CoV-2 infection due to their occupation or living situation. The study excluded those with history of confirmed SARS-CoV-2 infection or who were antibody positive at screening.

The analyzed population included the participants who received a negative reverse transcription polymerase chain reaction (RT-PCR) result at baseline. Participants were given either tixagevimab 150 mg plus cilgavimab 150 mg as 2 consecutive IM injections ($n = 3,441$) or 2 placebo IM injections ($n = 1,731$). The primary endpoint was symptomatic SARS-CoV-2 infection and a positive SARS-CoV-2 RT-PCR result during the 183 days of follow-up.

Once COVID-19 vaccines became available, participants could choose to be unblinded and receive the vaccine. Only the primary endpoints that occurred prior to unblinding or vaccine receipt were included in the analysis, resulting in a median follow-up of 83 days. Baseline characteristics were well balanced between the groups. RT-PCR-confirmed symptomatic SARS-CoV-2 infection that occurred prior to unblinding or vaccination was reported in 8 participants (0.2%) in the tixagevimab plus cilgavimab arm and in 17 participants (1.0%) in the placebo arm, representing a 77% reduction in the incidence of RT-PCR-confirmed symptomatic SARS-CoV-2 infection in the tixagevimab plus cilgavimab arm (95% CI, 46% to 90%; $P < 0.001$). A post hoc analysis performed after a median follow-up period of 6.5 months showed a similar reduction in the event rate between the study arms.

Thirty-five percent of the 3,461 tixagevimab plus cilgavimab recipients and 34% of the 1,736 placebo recipients experienced adverse events. Serious adverse events were reported in 1% of participants in both arms, with 1 participant from the tixagevimab plus cilgavimab arm reporting an anaphylactic

reaction that resolved with epinephrine therapy. Most adverse events were mild (73%) or moderate (24%), with similar incidences for mild and moderate adverse events between the arms. Serious cardiac adverse events occurred in 0.6% of participants in the tixagevimab plus cilgavimab arm and 0.2% of participants in the placebo arm. All participants who experienced a cardiac event had cardiac risk factors and/or a history of cardiac disease at baseline. There was no clear temporal pattern between these cardiac events and administration of the mAbs.

Additional Considerations

- Tixagevimab and cilgavimab have only been studied in clinical trials as a 1-time combination therapy; therefore, no safety or efficacy data exist for repeat dosing.
- The median follow-up time during the PROVENT trial was 83 days; therefore, the long-term duration of protection is not well defined.
- Tixagevimab plus cilgavimab is authorized for use as PrEP for a population that was not well represented in the PROVENT trial (i.e., a very small proportion of the participants in the trial were immunocompromised).
- The PROVENT trial has not been published.
- There are no data on the effectiveness of tixagevimab and cilgavimab in preventing infection from the Omicron variant.

References

1. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Evusheld (tixagevimab co-packaged with cilgavimab). 2021. Available at: <https://www.fda.gov/media/154701/download>.
2. Planas D, Saunders N, Maes P, et al. Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. *Nature*. 2021;Advance article preview. Available at: <https://www.nature.com/articles/d41586-021-03827-2>.
3. Cameroni E, Saliba C, Bowen JE, et al. Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift. *bioRxiv*. 2021;Preprint. Available at: <https://www.biorxiv.org/content/10.1101/2021.12.12.472269v1>.