

Operational Guidance for Tixagevimab/Cilgavimab

5/16/2022

This framework has been updated since April 14, 2022, to note that as supply has improved, providers do not need to restrict use to the clinical categories listed and may prescribe based on the U.S. Food and Drug Administration (FDA) emergency use authorization (EUA) eligibility criteria.

Introduction

On Dec. 10, 2021, the FDA issued an EUA to permit the emergency use of investigational monoclonal antibody (mAb) therapy products tixagevimab/cilgavimab (AZD7442) from AstraZeneca.¹ Unlike other mAb products currently under EUA, tixagevimab/cilgavimab is a long-acting mAb designed for use as a pre-exposure prophylactic (PrEP) medication only, administered in patients with moderate to severe immune compromise and those for whom “vaccination ... is not recommended due to a history of severe adverse reaction ...”²

With respect to PrEP use, the FDA has noted in the EUA for tixagevimab/cilgavimab:

“... it is reasonable to believe that EVUSHELD may be effective for use as pre-exposure prophylaxis of COVID-19 in certain adults and pediatric individuals (12 years of age and older weighing at least 40 kg), as described in the Scope of Authorization (Section II), and when used under the conditions described in this authorization, the known and potential benefits of EVUSHELD outweigh the known and potential risks of such product.”³

The patient eligibility criteria listed in the EUA are as follows.

“EVUSHELD may only be used in adults and pediatric individuals (12 years of age and older weighing at least 40 kg):

¹ [US Food and Drug Administration \(FDA\). Letter to Stacey Cromer Berman, PhD, AstraZeneca Pharmaceuticals LP, December 10, 2021. \(www.fda.gov/media/154704/download\)](https://www.fda.gov/media/154704/download)

² [FDA. FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR EVUSHELD™ \(tixagevimab co-packaged with cilgavimab\). December 2021. \(www.fda.gov/media/154701/download\)](https://www.fda.gov/media/154701/download)

³ [FDA. Letter to Stacey Cromer Berman, PhD, AstraZeneca Pharmaceuticals LP, December 10, 2021. \(www.fda.gov/media/154704/download\)](https://www.fda.gov/media/154704/download)

- Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 and
- Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination or
- For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s)."⁴

The U.S. government has secured supplies of this investigational antibody therapy for distribution to states. Allocation and administration of this mAb for PrEP is a potentially important means of conferring long-term protection to immunocompromised patients who have already received their COVID-19 vaccine series.

This document provides interim ethical guidance regarding the allocation of tixagevimab/cilgavimab. Based on federal guidance, it is anticipated that tixagevimab/cilgavimab will initially be in very short supply: Only about 1,600 doses are expected for disbursement in the first month (approximately 800 doses in each of weeks one and three of distribution). According to a survey of facilities in Minnesota, sites expect as many as 250,000 or more patients to qualify for tixagevimab/cilgavimab under the EUA. **This guidance addresses allocation of tixagevimab/cilgavimab in the early stage of distribution, when supply is especially scarce.**

As production of tixagevimab/cilgavimab increases and more facilities offer appointments, inventory and appointments may become sufficient to meet need. **When the inventory of tixagevimab/cilgavimab and availability of appointments are sufficient or when this mAb becomes commercially available with sufficient appointment slots** (i.e., moving out of the allocation approach outlined below), standard clinical ethical values guiding competent medical care, shared decision-making with patients, and appropriate stewardship of medications apply.

The document addresses relevant past guidance developed at MDH, key ethical values, and how allocation should occur both under conditions of scarcity and conditions of sufficient supply regarding: (1) allocation to facilities throughout the state and (2) allocation among patients within each facility.

Ethical criteria for distribution and allocation of tixagevimab/cilgavimab

Ethical strategy for distribution throughout the state

The EUA specified that AstraZeneca will provide supplies of mAbs to the federal government for distribution directly to hospitals by authorized distributors.

Especially when supply of the resource is very limited, MDH **will distribute tixagevimab/cilgavimab to academic health centers and other health care facilities that have an ongoing relationship with substantial cohorts of immunocompromised patients (e.g., cancer centers or transplant-care clinics)**, given clinical eligibility specified in the EUA for the drug. Further, access to tixagevimab/cilgavimab will **not** be allocated through the Minnesota

⁴ FDA. Letter to Stacey Cromer Berman, PhD, AstraZeneca Pharmaceuticals LP, December 10, 2021. (www.fda.gov/media/154704/download)

Resource Allocation Platform (MNRAP), an MDH website that connects COVID-19-positive patients with facilities infusing other COVID-19 monoclonal antibodies, given that the clinically eligible patients typically have a usual source of care for their immunocompromising condition.

If an immunocompromised patient has no usual source of care or has a source of care that is not one of the sites receiving tixagevimab/cilgavimab, those sites receiving the resource should accept new patient intake requests associated with the use of and monitoring for tixagevimab/cilgavimab. **It is inequitable for facilities to treat only established patients, thus disadvantaging patients who are not affiliated with any of the facilities currently receiving distribution of the resource.**

Each region should have at least one location designated for tixagevimab/cilgavimab administration, taking into account geographic factors and populations' needs in order to promote equitable access.

Allocation to facilities will proceed as follows:

- Within regions, MDH will allocate doses of tixagevimab/cilgavimab to facilities proportionate to the number of clinically eligible patients who are Minnesota residents (since each state will receive its own allocation from the federal government). Allocation will account for the facilities' capacities to administer, track, and report patient-level outcomes for tixagevimab/cilgavimab. Allocation will also take into account previous allocations to sites, compliance with MDH reporting standards, and adherence to ethical standards outlined in this guidance.
- Facilities should not overestimate or otherwise inflate patient estimates. Facilities that do so may be excluded from subsequent allocations by MDH until such time as their clinically eligible patient counts are deemed precise and accurate. In such a case, MDH will adjust distribution within regions to promote continued access for affected patients.
- All treating facilities are required to complete the federally required daily reporting of both inventory and number of patient courses (or doses) allocated to patients to be eligible for state allocation. Failure to accurately report these data affects the entire state allocation the federal government will grant Minnesota.

Regional Health Care Coalitions may ask facilities to redistribute doses between treating facilities in the same region, but facilities should not independently redistribute doses. **This also means systems and facilities should not distribute doses to facilities outside the region or state without express permission from MDH.**

Ethical strategy for allocation among patients

Given that significant scarcity is expected in the early stages of allocation, **providers should counsel at-risk patients who may not receive allocation of this resource about the importance of seeking early treatment with mAbs or oral antivirals if they test positive for COVID-19.** Information about mAbs may be found at [Therapeutic Options for COVID-19 Patients \(www.health.state.mn.us/diseases/coronavirus/hcp/therapeutic.html\)](http://www.health.state.mn.us/diseases/coronavirus/hcp/therapeutic.html). Additional layered mitigation efforts, such as vaccination of close contacts, masking, and social distancing are advisable and should be recommended for this high-risk group.

The following patients are clinically eligible for tixagevimab/cilgavimab under the EUA.⁵

⁵ FDA. FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR EVUSHELD™ (tixagevimab co-packaged with cilgavimab). December 2021. (www.fda.gov/media/154701/download)

Adults and pediatric individuals (12 years of age and older weighing at least 40 kg):

- Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to a person infected with SARS-CoV-2 and;
- Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination or;
- For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).

Per the EUA, the medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination include but are not limited to:

- Active treatment for solid tumor and hematologic malignancies.
- Receipt of solid organ transplant and taking immunosuppressive therapy.
- Receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within two years of transplantation or taking immunosuppression therapy).
- Moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome).
- Advanced or untreated HIV infection (people with HIV and CD4 cell counts less than 200/mm³, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV).
- Active treatment with high-dose corticosteroids (i.e., more than 20 mg prednisone or equivalent per day when administered for two weeks or longer); alkylating agents; antimetabolites; transplant-related immunosuppressive drugs; cancer chemotherapeutic agents classified as severely immunosuppressive; tumor-necrosis (TNF) blockers; and other biologic agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents).⁶

Under scarcity conditions, facilities should allocate tixagevimab/cilgavimab among clinically eligible patients in a way that maximizes the number of lives saved, taking into account both risk and expectation of benefit, while respecting individuals and groups and protecting against inequity. **In the first stage of distribution, when supply of the resource is especially scarce, facilities should prioritize eligible patients at highest risk of poor outcomes if they were to develop COVID-19.** While the EUA does not provide clinical priorities among the listed eligible groups, MDH has consulted with expert clinical advisors in the state to identify patients at highest clinical priority. The clinical priorities identified in this process will be revised as further information becomes available, or if the federal government issues guidance about clinical priorities for tixagevimab/cilgavimab.

In the early stage of distribution (until additional guidance is issued), facilities should allocate as follows (please refer to the Appendix for a list of clinical categories):

- Prioritize patients in the following groups: patients in Category 1 should be prioritized over those in Category 2 (and so on through the list of categories). All patients within each category should be taken to have equivalent priority – the bulleted list within each category does not present an ordering of priority for allocation.

⁶ FDA. FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR EVUSHELD™ (tixagevimab co-packaged with cilgavimab). December 2021. (www.fda.gov/media/154701/download)

- **Among similarly situated patients, randomize allocation.** Randomization is the fairest process for allocating among patients who are similarly situated in terms of risk. Prioritizing based on first-come, first-served or on pre-existing relationship with the treatment facility creates inequities, because these approaches provide advantage to privileged populations.
- A facility's randomization process should thus include eligible patients seeking access who are not affiliated with the facilities currently receiving supply of this resource.
- Allocation decisions should **consider whether the patient is imminently and irreversibly dying or terminally ill with life expectancy under six months** (e.g., eligible for admission to hospice). If supply of tixagevimab/cilgavimab is scarce, patients in this group should not receive priority for access. If supply is sufficient, then patients who are terminally ill with life expectancy under six months should be considered as candidates for this mAb.

As supply increases, the state will be able to expand allocation to more of the patients listed in the EUA as clinically eligible for this resource.

Access

Patients may seek access to this mAb as follows: Facilities selected to dispense tixagevimab/cilgavimab should identify patients who are eligible for treatment under the terms of the EUA and the priority categories identified by MDH. Following the randomization process described above, selected patients should be contacted by the treating facility. Patients may also be referred by their primary care provider or health system that is providing treatment for their immunocompromising condition to facilities selected to dispense tixagevimab/cilgavimab. Patients referred to treatment facilities in this way should be included in the allocation process without any disadvantage.

Patient ability to pay should not control access to tixagevimab/cilgavimab, under circumstances of scarce or sufficient supply. Treatment facilities (or the health care systems/organizations with which they are affiliated) should work with patients to identify sources of payment for tixagevimab/cilgavimab, including based on patient eligibility for insurance, subsidized care, or any program that will enable access. Note that the ability to pay relates not only to the cost of the mAb (which has initially been provided free of charge through the federal government), but also related injection-associated costs, such as provider reimbursement and facility fees. Fair access to tixagevimab/cilgavimab will also depend on effective messaging to diverse populations in the state about the availability of this mAb and on the willingness of treating facilities to accept referrals for new patients from outside their systems to provide tixagevimab/cilgavimab and follow-up for patients who lack a regular primary care provider or a system that can administer tixagevimab/cilgavimab.

Patient decision-making and consent to tixagevimab/cilgavimab

Under all circumstances – scarce or sufficient supply – patients who are capable of decision-making are entitled to partner with their care team in deciding whether to consent to administration of tixagevimab/cilgavimab. For patients who are not capable of making decisions, their authorized decision-maker should be consulted. Facilities should offer patients sufficient information to allow them to decide whether to seek tixagevimab/cilgavimab, including information regarding alternatives and whether receiving this mAb may limit their access to other interventions or research studies. At the treating facility, informed consent conversations will occur immediately prior to injection. To promote equity, consent forms/patient information sheets should be available in the diverse languages of a facility's patient populations, and appropriate translation services should be available during screening and upon presentation at the facility in order to foster appropriate consent discussions. The authorized decision-maker should be the person appointed by the patient (or otherwise authorized by law) to make decisions on their behalf. If the patient has not indicated who that person should be, the clinical team should work with the

patient's spouse, partner, family, or close friend. All personnel involved in patient decision-making processes should work to follow Minnesota guidance and law on surrogate decision-making. If patients or their authorized decision-makers express interest in accessing mAb treatment, but have concerns about ability to pay, treating facilities (or the health care systems/organizations with which they are affiliated) should work with patients to identify sources of payment for mAbs.

Allocation decisions

Access to and allocation of tixagevimab/cilgavimab **must comply with state and federal laws that prohibit discrimination** on any basis. For a resource on federal civil rights protections and guidance, providers may refer to the U.S. Department of Health and Human Services [Civil Rights and COVID-19 \(www.hhs.gov/civil-rights/for-providers/civil-rights-covid19/\)](http://www.hhs.gov/civil-rights/for-providers/civil-rights-covid19/). A resource on state nondiscrimination law is the Minnesota Department of Human Rights' [Your Civil Rights \(mn.gov/mdhr/yourrights/\)](http://mn.gov/mdhr/yourrights/).

Importance of documentation and reporting

Patients who receive this mAb should have an order and treatment notes documented in the patient's health record. MDH will conduct routine audits for quality improvement purposes to determine if this framework or its operationalization require refinement to meet the fundamental moral commitments and objectives guiding mAb allocation.

Appendix

Prioritization of patients for tixagevimab/cilgavimab

This prioritization was developed by an advisory group of subject matter experts in infectious disease, transplant, oncology, and pediatrics in the state of Minnesota, in collaboration with the Minnesota Department of Health. This prioritization is based on expert opinion, as there is limited data available to differentiate degrees of risk between patients with different types of immunocompromising illness. These categories are subject to change, based on further revision and additional guidance from professional societies as it becomes available. SARS-CoV-2 antibody testing was not included as a means of prioritizing patients, due to a lack of data on the degree of protection and correlates of immunity with various serological assays.

As of April 25, 2022, due to improved supply, MDH is no longer recommending that providers restrict use of tixagevimab/cilgavimab to the high-risk categories listed here. As long as supply remains adequate to ensure that patients at highest risk can continue to access treatment, providers may evaluate and prescribe for patients based on eligibility criteria listed by the FDA.

Category 1 (highest risk)

- Lung transplant recipient (any time frame).
- Small bowel transplant recipient (any time frame).
- Receipt of the following immunosuppressive medication within the past 12 months (including for solid organ transplant).
 - Antithymocyte globulin (ATG).
 - Alemtuzumab.
 - Anti-B-cell therapy (e.g., rituximab).
- B-cell malignancies, on active treatment (e.g., B-cell lymphomas, chronic lymphocytic leukemia, acute B-cell lymphoblastic leukemia, etc.).
- Multiple myeloma, on active treatment with two or more agents.
- Allogeneic stem cell transplant, within 12 months of transplant.
- Autologous stem cell transplant, within six months of transplant.
- Receipt of anti-CD19 or anti-BCMA (CAR)-T-cell immunotherapy, within six months of treatment.
- Primary or secondary T-cell immunodeficiency, including severe combined immunodeficiency.
- Recipient of more than one active transplant, different organs (any time frame).
 - Example: kidney-pancreas, heart-kidney.
- Acute myeloid leukemia under active treatment.
- Additional pediatric conditions to be considered as Category 1 (age 12-17):
 - Combined immune deficiencies with or without immune dysregulation (e.g., APDS, STAT3 GOF, ALPS).
 - Primary immune regulatory disorders with or without immune deficiency (e.g., APECED, XIAP).
 - High-risk or relapsed acute lymphoblastic leukemia/lymphoblastic lymphoma on intensive therapy (not maintenance therapy).

Category 2

- Any solid organ transplant within the past 12 months from date of transplant, not otherwise eligible in Category 1.
- Allogeneic stem cell transplant, more than 12 months since transplant (and not more than two years from transplant UNLESS still on immunosuppressive therapy, per the EUA criteria).
- Autologous stem cell transplant, more than six months since transplant (and not more than two years from transplant UNLESS still on immunosuppressive therapy, per the EUA criteria).

Category 3

- Any solid organ transplant recipient more than 12 months since transplant.
- Any solid tumor, on active myelosuppressive chemotherapy.
- Multiple myeloma, on maintenance therapy.

Category 4

- Active treatment with high-dose corticosteroids (i.e., more than 20 mg prednisone or equivalent per day when administered for two weeks or longer).
- Active treatment with other agents that are immunosuppressive or immunomodulatory, not otherwise listed in Categories 1-3.
- Advanced or untreated HIV infection.
 - HIV with CD4 less than 200/mm³ (if aged less than 14 years, CD4% less than 15%).
 - AIDS-defining illness.

Category 5

- Persons for whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended, due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).



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