STAY SAFE MN

Operational Guidance for Monoclonal Antibodies

3/3/2022

This guidance has been updated since Feb. 4, 2022, to incorporate the newly authorized monoclonal antibody bebtelovimab.

Introduction

Since November 2020, the U.S. Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUAs) to permit the emergency use of investigational monoclonal antibody (mAb) therapies for the treatment of mild to moderate COVID-19 in adult and pediatric patients.

The only currently authorized mAbs for the treatment of acute COVID-19 are sotrovimab and bebtelovimab. **Providers should note that bebtelovimab is only authorized for use in people "for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate."**[1]

This document provides the Minnesota Department of Health's (MDH's) guidance for access to mAbs for eligible patients. It also explains the methods used when the supply of mAbs is insufficient to meet the need among eligible patients. This guidance and those methods are incorporated into a centralized system called the Minnesota Resource Access Platform (MNRAP).[2] Previous MDH guidance documents on access to mAbs, including "Ethical Framework for Allocation of Monoclonal Antibodies during the COVID-19 Pandemic," are superseded by this document.

As detailed below in Sections C through E, the ability to provide mAbs access to patients who meet minimum EUA eligibility criteria depends upon the relationship between the available supply and the identified demand. Access for eligible patients is contingent on which of three supply-dependent stages is in effect. The three stages are:

- Stage 1, when supply and/or appointment capacity is sufficient to meet the demand of all who are eligible.
- Stage 2, when supply and/or appointment capacity is insufficient for all who are clinically eligible, requiring deprioritization of those at lower clinical risk. This will begin with deprioritization of non-pregnant patients

[1] FDA. Fact Sheet for Healthcare Providers: EUA for Bebtelovimab. (www.fda.gov/media/156152/download)

[2] Some health systems have opted out of MNRAP, but those systems are expected to operate their approaches with similar principles as MNRAP and must accept unaffiliated patients without disadvantaging them relative to affiliated patients. Accordingly, these guidelines are applicable to opted out and opted in systems alike, such that the selection processes should account for the same clinical and nonclinical factors as outlined in this guidance. Opted-out systems should also meet additional reporting requirements set by MDH to demonstrate their respective systems are performing as intended.

with M-MASS scores of 0, followed by deprioritization of non-pregnant patients with M-MASS scores of 1, 2 and 3.

- Stage 3, when supply and/or appointment capacity is insufficient even for those patients with a M-MASS score of 4 or higher (or who are pregnant), requiring weighted random selection among only those patients.

A. General Guidelines for Providers

1. Confirm clinical eligibility

Whether supply and appointment availability are scarce or sufficient, the allocation of mAbs to a patient through the MNRAP system or through non-participating health systems is provisional because patients must undergo confirmatory screening when scheduled for their appointment, or at time of infusion/injection. Confirming eligibility prior to time of infusion/injection is preferable, as it would prevent having to turn away patients who appear for infusion/injection appointments, if their confirmatory screening indicates that they are not clinically eligible. Those who are not clinically eligible would not receive mAbs.

2. Patient decision-making and consent to mAbs

Under all circumstances – scarce or sufficient supply of therapies or appointments – **patients who are capable of decision-making are entitled to partner with their care team in deciding whether to consent to administration of mAbs**. For patients who are not capable of making decisions, their authorized decision-maker should be consulted. When patients are provisionally screened for eligibility to receive mAbs and selected to receive the resource through MNRAP, they should be informed whether they have been deemed eligible for and have been allocated a course of mAbs.

The MNRAP centralized screening website provides patients with information about mAbs, including that they are not FDA-approved, but are available under an EUA. The website also offers patients sufficient information to allow them to decide whether to seek mAbs, including information regarding alternatives and whether receiving mAbs may limit their access to other interventions or research studies.

At the infusion/injection facility, informed consent conversations will occur immediately prior to infusion/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

3. Importance of documentation and confidentiality

All information provided by patients in the screening process must be treated as **private patient data** and available only to MDH, the relevant health care system and hospital, and the infusion/injection facility. Under all circumstances – scarce or sufficient supply – patients who receive mAbs should have an order and treatment notes documented in the patient's health record. In addition, allocation decisions should be recorded by the care setting in a **facility-wide log** to allow for transparency and retrospective review. Under conditions of scarcity, when mAbs are allocated via triage, this log should include which patients were eligible for mAbs, which patients received the mAb allocation, and how randomization occurred.

MDH will conduct routine audits for quality improvement purposes and to determine attainment of program objective.

B. Determining whether supply of mAbs is sufficient or scarce

MDH determines whether mAbs are in sufficient or scarce supply by region within Minnesota at least weekly. Determining scarcity depends on the number of courses of mAbs available (inventory) and the number of appointment slots available to administer the mAbs (capacity), including health systems that have opted out of the MNRAP platform. To determine scarcity, MDH projects the need for mAbs for the coming week, by considering the number of patients treated with mAbs in the previous week and adjusting for trends in case incidence rates as well as demand.

MAbs are in **scarce supply** statewide when either the number of courses available or the infusion and injection appointments available are less than 125% of the projected number of doses of mAbs needed for the coming week.

MAbs are in **sufficient supply** when both medication quantity and available infusion/injection appointments meet or exceed 125% of MDH's projection of need.

Projections of demand relate to the allowable level of clinical prioritization (refer to "Stage 2: Clinical prioritization" below), e.g., demand would be calculated only from patients with a clinical prioritization score of X (when X=the current level of prioritization) or higher, and not of ALL patients seeking treatment. Only when it is expected that supply will not meet demand for patients deemed high risk under the clinical prioritization criteria below will a weighted random selection process be considered.

Determination of scarcity or sufficiency considers the entire week and is not based only on scarcity on the weekend due to the lack of providers offering appointments on the weekend. A weighted random selection process will not be triggered based only on the fact that some patients who are clinically eligible cannot find appointments during Saturday or Sunday. Facilities are encouraged to provide adequate access and appointments on weekends as well as weekdays.

C. Stage 1: Sufficient supply means access is based on clinical eligibility

When there is a **sufficient supply** of mAbs (including, as outlined above, sufficient inventory as well as appointments), the resource is allocated in line with competent medical care, shared decision-making with patients, and appropriate stewardship of medications. The centralized MNRAP screener assesses provisional clinical eligibility for the resource and provides referrals to facilities for all provisionally eligible patients. For patients being cared for by health care systems that have opted out of MNRAP, their health care system will perform this function.

1. Determine clinical eligibility based upon EUA criteria

Providers must be familiar with the EUAs for the currently authorized mAbs. The below and any quotations in this section are from the Sotrovimab EUA factsheet.[3] Generally, mAbs are authorized for the "treatment of mild to moderate COVID-19 in adults and pediatric patients (12 – 17 years of age weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19, including hospitalization or death" but are not authorized for use in patients "who are hospitalized due to COVID-19, OR who require oxygen therapy due to COVID-19, OR who require an increase in baseline oxygen flow rate due to COVID-19 (in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity)." The EUAs explain that "The following medical conditions or other factors may place adults and pediatric patients […] at higher risk for progression to severe COVID-19:"

- Older age (for example 65 years of age and older).
- Obesity or being overweight (for example, adults with BMI greater than 25 kg/m2, or if ages 12-17, a BMI at or greater than the 85th percentile for their age and gender based on CDC: Clinical Growth Charts (www.cdc.gov/growthcharts/clinical_charts.htm).
- Pregnancy.
- Chronic kidney disease.
- Diabetes.
- Immunosuppressive disease or immunosuppressive treatment.
- Cardiovascular disease (including congenital heart disease) or hypertension.
- Chronic lung diseases (for example, chronic obstructive pulmonary disease; asthma, moderate to severe; interstitial lung disease; cystic fibrosis; and pulmonary hypertension).
- Sickle cell disease.
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies).
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation not related to COVID-19).

The Sotrovimab EUA further states that:

"Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of [monoclonal antibody therapies] under the EUA[s] [are] not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: People with Certain Medical Conditions (www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html). Healthcare providers should consider the benefit-risk for an individual patient."

Finally, the EUAs provide that mAbs should be administered as soon as possible after a positive viral test for SARS-CoV-2 and within 7 days of symptom onset.

[3] FDA. December 2021. Fact Sheet for Healthcare Providers Emergency Use Authorization (EUA) of Sotrovimab. (www.fda.gov/media/149534/download)

2. Additional Considerations for Providers

As stated in the EUAs, providers are encouraged to review the CDC's People with Certain Medical Conditions (www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html) and Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Providers (www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html).

Patients being considered for mAbs must have a COVID-19 infection confirmed either by PCR or by antigen testing. Home tests may be used if the patient can provide proof of the positive result. Patients must also have at least one COVID-19 symptom.

Patients who have been vaccinated for COVID-19 should remain eligible for mAbs if they develop breakthrough infections and unvaccinated patients should not be penalized.

Providers should **consider whether the patient is imminently and irreversibly dying or terminally ill with life expectancy under 6 months** (e.g., eligible for admission to hospice). If supply is sufficient, then patients who are terminally ill with life expectancy under 6 months should be considered as candidates for mAbs.

Access to and allocation of mAbs **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/). A resource on state nondiscrimination law is the Minnesota Department of Human Rights' Your Civil Rights (mn.gov/mdhr/yourrights/).

D. Stage 2: Clinical prioritization when supply is constrained

1. M-MASS: modified Monoclonal Antibody Screening Score

At this time, the EUAs identify which types of patients are eligible and ineligible for mAbs, but do not offer sufficient clinical information to construct clinical priority tiers – this is why MDH's **MNRAP uses the modified Monoclonal Antibody Screening Score (M-MASS)** to prioritize among eligible patients. This score is adapted from Mayo Clinic's published studies.[4,5]

The M-MASS is calculated as follows: on a scale of 0-19: age 65 years and older (2 points), BMI 35 kg/m^2 and higher (2), diabetes mellitus (2), chronic kidney disease (3), cardiovascular disease in a patient 55 years and older (2), chronic respiratory disease in a patient 55 years and older (3), hypertension in a patient 55 years and older (1), and immunocompromised status (4).

[4] Bierle et al., Monoclonal Antibody Treatment of Breakthrough COVID-19 in Fully Vaccinated Individuals with High-Risk Comorbidities. 2021 MedRxiv (www.medrxiv.org/content/10.1101/2021.10.19.21265222v1)

[5] Razonable, R. R., Ganesh, R., & Bierle, D. M. (2022). Clinical Prioritization of Antispike Monoclonal Antibody Treatment of Mild to Moderate COVID-19. In Mayo Clinic Proceedings (Vol. 97, Issue 1, pp. 26–30). Elsevier BV (doi.org/10.1016/j.mayocp.2021.11.017)

2. Prioritized access based upon M-MASS score

When escalating prioritized allocation to mAbs, sites should begin by deprioritizing access for clinically eligible patients with the lowest clinical risk. **These patients are not EXCLUDED**, but only given access to appointments after higher-risk patients have been scheduled. This strategy ensures that all higher risk patients are allocated mAbs before lower risk patients have access.

Additionally, patients who are pregnant are clinically prioritized, independent of their M-MASS score. Sites deprioritize low M-MASS scores for non-pregnant people in response to appointment scarcity. This means MNRAP[6] begins by deprioritizing access for non-pregnant patients with a M-MASS of 0, and then is ready to deprioritize M-MASS=1, M-MASS=2, and M-MASS=3 as scarcity deepens.

- MNRAP tracks all patients that have been deprioritized for access and, at the end of each daily allocation cycle, allocates any available appointments to these deprioritized patients in order of clinical priority, randomizing access for similarly rated patients (refer to "Employing an end-of-day holdback or reserve" below). To promote fairness across systems, opted-out sites should do the same.
- If supply is too scarce to allow allocation to all patients M-MASS=4 or higher OR pregnant, then allocation will be managed via weighted random selection as described below. M-MASS of 4 is considered the point beyond which patients are judged to have a high risk (i.e., 10% or higher) of severe COVID-19 outcomes.

This clinical prioritization does not apply to patients aged younger than 18 years.

E. Stage 3: Instant-read weighted random selection when supply is scarce

When scarcity exists such that mAb access cannot be provided to all patients that have a modified Monoclonal Antibody Screening Score (M-MASS) score of 4 or more OR patients who are pregnant mAbs will be allocated to patients 18 years of age and older via a **weighted random selection mechanism, using the centralized MNRAP screening website** managed by MDH (unless the patient is accessing mAbs through an opt-out health care system, which will run its own weighted random selection process that should meet the requirements of this document). **Patients younger than 18 will be directed to pediatric providers** who will determine whether mAbs may be safe and effective for them, given considerations specific to patients in this population, but otherwise will not participate in any weighted random selection process.

The weighted random selection mechanism should operate as follows:

- All clinically eligible patients will have a base chance of receiving mAbs when scarce, with that chance calculated by available supply and predicted demand for the day the patient submits the screener on the MNRAP platform.

By default, supply (inventory and appointments) will be divided into one-seventh the weekly allocation for use on a daily basis. This daily allocation will be set at the beginning of the week, and the platform will calculate necessary adjustments from default based on assessments of expected growth or decline in case incidence over

[6] After Dec. 1, 2021, sites that have opted out of MNRAP and are running their own screening processes are encouraged to use the same M-MASS scoring system and deprioritization of non-pregnant M-MASS=0 patients as implemented by MNRAP. If scarcity deepens and deprioritization of non-pregnant M-MASS=1, M-MASS=2, or M-MASS=3 is implemented by MNRAP, opted-out sites using the M-MASS scoring systems should be prepared to do the same.

the course of the coming week. Any supply that remains unobligated at the end of a day will be rolled over for the next day's use. Facilities should report how many days a week they are open for infusions/injections to MDH to reflect their daily allocation more accurately.

Infusion/injection facilities should report to MDH daily the number of doses delivered to patients. The MNRAP screening website will allocate doses of mAbs, both in circumstances of scarcity and when inventory and capacity are not scarce. That is, approximately one-seventh of the week's pool should be made available each day, with any leftover added to the following day. This will avoid running out of doses in the first several days after a shipment during scarcity, which would disadvantage patients who seek care later in the week. If facilities do not operate each day of the week, their weekly supply will be divided evenly over the number of days in operation, as above, and when in operation, facilities are expected to have daily capacity to meet the assigned number of infusions/injections.

Employing an end-of-day holdback or reserve

Under conditions of constrained supply or scarcity when the Stage 2 clinical prioritization strategy is active or the Stage 3 MNRAP weighted random selection process is operational, the MNRAP system will initially employ an **end-of-day holdback** to mitigate inequities associated with system startup. The fairness of the weighted random selection process depends upon the accuracy of the modeling built into the system to predict demand for mAbs throughout the course of the week. If the prediction is inaccurate – as it very likely will be, given the number and types of variables that affect when patients might use the screener – patients who are similarly situated (and so should receive roughly equivalent chances at allocation) would, in reality, have varying chances. To mitigate this equity risk, everyone who does not get selected over the course of the day will get a second chance overnight, using supply that will be held back for this purpose (holdback size to be determined by MDH).

Patients receiving provisional selection for mAbs on their second chance will automatically be matched with providers that have infusion/injection capacity (which may include opt-out systems). As with the instant weighted random selection function, electronic referrals from the holdback allocation are automatically be sent to the facility, which then calls the patient to schedule.

Patients who do not receive mAbs in either their first or second chance will remain in the pool for additional chances against future end-of-day holdbacks until their eligibility window expires. They may also be considered by opted-out sites during this time. Patients do not need to 're-enter' MNRAP for additional attempts at randomization in later days.

Handling differential demand through the weighted random selection process

MNRAP will set the probability of provisional selection for accessing mAbs based on supply of medication and infusion/injection slots relative to **predicted** demand. If the demand is much lower than expected, it is plausible that patients will be told they were not selected for scarcity reasons when, in fact, by the end of the day there is still supply left. A feature of the end-of-day holdback above is that these patients will be selected during their second chance if they are clinically eligible (since supply exceeds demand). A more problematic scenario is if demand is much higher than expected; in that case, supply will be depleted before the end of the day. Patients who access the MNRAP screener after supply has been depleted will be considered in the end-of-day holdback only.

Appendix

Therapeutic Options for COVID-19 Patients (www.health.state.mn.us/diseases/coronavirus/hcp/therapeutic.html)
Information and resources on mAb treatment.

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