PENNSYLVANIA DEPARTMENT OF HEALTH
2021 – PAHAN – 575 – 6-3-ADV

ADVISORY: COVID-19 Treatment Options

DATE:	6/3/2021
TO:	Health Alert Network
FROM:	Alison V. Beam, JD, Acting Secretary of Health
SUBJECT:	**COVID-19 Treatment Options**
DISTRIBUTION:	Statewide
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COUNTY:	n/a
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This transmission is a "Health Advisory," and provides important information for a specific incident or situation; may not require immediate action.

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- With the ongoing threat of COVID-19, providers are encouraged to consider all options for COVID-19 treatment.
- The FDA has issued Emergency Use Authorizations (EUAs) for anti-SARS-CoV-2 monoclonal antibodies, combination therapies **bamlanivimab** plus **etesevimab** and **casirivimab** plus **imdevimab**, and **sotrovimab** for use in non-hospitalized patients (age≥12 and weighing≥40kg), with laboratory confirmed SARS-CoV-2 infection and mild-to-moderate COVID-19 disease who are at high risk of progressing to severe disease and/or hospitalization.
    - **Bamlanivimab** by itself no longer has an EUA as of 4/16/21, due to emerging data regarding SARS-CoV-2 viral variants' resistance to this agent when used alone.
    - It is recommended to administer these drugs as soon as possible after a positive SARS-CoV-2 test result, and within 10 days of symptom onset.
- **Remdesivir** continues to be the only FDA approved drug for the treatment of hospitalized patients with COVID-19 who require supplemental oxygen.
- **Dexamethasone**, and its equivalent corticosteroids, continues to be recommended for hospitalized patients who require mechanical ventilation; the greatest improvement of survival is shown in this group, and to a lesser degree in hospitalized patients who require supplemental oxygen. If corticosteroids are contraindicated, **baricitinib** plus **remdesivir** may be used.

Pennsylvania Department of Health (DOH) provides this guidance based on available information about COVID-19 and is subject to change.

Although case counts are declining in Pennsylvania, COVID-19 cases and COVID-19-related hospitalizations continue to occur. The Pennsylvania DOH aims to provide healthcare providers (in both inpatient and outpatient settings) an outline of the current options available for treatment of COVID-19.

This advisory is an update to HAN 565 and includes additional information about sotrovimab. The DOH would also like to inform healthcare providers that availability of these treatment products has increased. Since insurance coverage for treatment remains mandated by federal law, healthcare providers are encouraged to utilize the treatment options, when clinically appropriate, with the goal of reducing hospital admissions and/or duration of hospitalizations, and the overall COVID-19 burden in the community. Additionally, the guidance for the treatment options has changed; the DOH seeks to relay the current guidance to healthcare providers and provide additional reference material. The treatment options and current guidance is outlined below.

A. COVID-19 treatment options based on setting and severity of disease

COVID-19 disease is thought to be driven by two main processes.

- Early disease course
  - Driven by replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
  - *Anti-SARS-CoV-2 antibody-based therapies* (monoclonal antibodies*)* are recommended for use in **outpatient settings**, and are most effective if used in the early stages of COVID-19 disease because the host has not yet mounted an effective immune response to the virus. The FDA has issued Emergency Use Authorizations (EUAs) for certain anti-SARS-CoV-2 monoclonal antibodies. Options include the following combination therapies:
    - **Bamlanivimab** plus **etesevimab**
      - **Note: bamlanivimab**'s monotherapy EUA was revoked by the FDA as of 04/16/21, due to emerging data regarding SARS-CoV-2 viral variants' resistance to this agent when used alone.
    - **Casirivimab** plus **imdevimab**
    - **Sotrovimab** (as of 5/26/21)
    - The above recommendations are based on preliminary data (from Phase 1 and 2 clinical trials (and also Phase 3 for sotrovimab)) which suggests that individuals in the outpatient setting may benefit from receiving anti-SARS-CoV-2 monoclonal antibodies early in the course of the disease.
    - While not required, healthcare providers are encouraged to discuss with patients about participation in anti-SARS-CoV-2 monoclonal antibody clinical trials; Phase 3 randomized controlled trials would further inform monoclonal antibody treatment recommendations/generally advance knowledge of the effectiveness of these treatments.
    - Shared decision making between the patient and clinician is appropriate for high-risk patients who meet EUA criteria for treatment with monoclonal antibodies, especially to discuss the potential benefits and risks of the treatments.
    - See further details about the treatments and their criteria for use in Section B.
  - *Antiviral therapies* are believed to have the greatest benefit if administered early in the disease course
    - **Remdesivir**: an antiviral agent, currently the only FDA approved drug for the treatment of COVID-19
      - Recommended use: **hospitalized patients who require supplemental oxygen.**
      - Not routinely recommended for: patients who require mechanical ventilation (there is currently a lack of data showing benefit of its use at this advanced stage of disease)
- Late disease course
  - Driven by a severe immune/inflammatory response to the virus, leading to tissue damage
  - *Immunosuppressive/anti-inflammatory therapies* are likely more beneficial in the late stage of disease
    - **Dexamethasone**: a corticosteroid, improves survival to the greatest effect in *hospitalized patients who require mechanical ventilation*, and to a lesser degree in hospitalized patients who require supplemental oxygen
      - If dexamethasone is not available, alternative corticosteroids such as prednisone, methylprednisolone, or hydrocortisone can be used.

- In the rare event that corticosteroids are contraindicated, **baricitinib** plus **remdesivir** can be used. The FDA has issued an EUA for baricitinib use in combination with remdesivir for these circumstances.
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B. Anti-SARS-CoV-2 monoclonal antibody treatment, additional details:

The FDA has issued Emergency Use Authorizations (EUAs) for certain anti-SARS-CoV-2 monoclonal antibodies, combination therapies **bamlanivimab** plus **etesevimab** and **casirivimab** plus **imdevimab**, and monotherapy **sotrovimab**. The EUAs allow for use of the agents in patients who meet the following criteria:

- Non-hospitalized patients.
- Age 12 or older, and weighing 40 kg or more.
- Laboratory confirmed SARS-CoV-2 infection (PCR test).
- Mild-to-moderate COVID-19 disease who are at high risk of progressing to severe disease and/or hospitalization (see treatment EUAs for details on high risk criteria).
- It is recommended that these drugs be administered as soon as possible after a positive SARS-CoV-2 test result, and within 10 days of symptom onset.
- The issuance of an EUA does not constitute FDA approval.

Bamlanivimab (also known as LY-CoV555 and LY3819253) and **etesevimab** (also known as LY3832479 and LY-CoV016) are neutralizing IgG1 monoclonal antibodies that bind to distinct but overlapping epitopes within the receptor binding domain (RBD) of the spike protein of SARS-CoV-2. The monoclonal antibodies are administered intravenously together as a combined one-time infusion of Bamlanivimab 700 mg and etesevimab 1,400 mg.

Casirivimab (previously REGN10933) and **imdevimab** (previously REGN10987) are recombinant human monoclonal antibodies that bind to nonoverlapping epitopes of the spike protein receptor binding domain (RBD) of SARS-CoV-2. The combination of these two antibodies blocks the binding of the RBD to the host cell. The monoclonal antibodies are administered intravenously together as a combined one-time infusion of casirivimab 1,200 mg and imdevimab 1,200 mg.

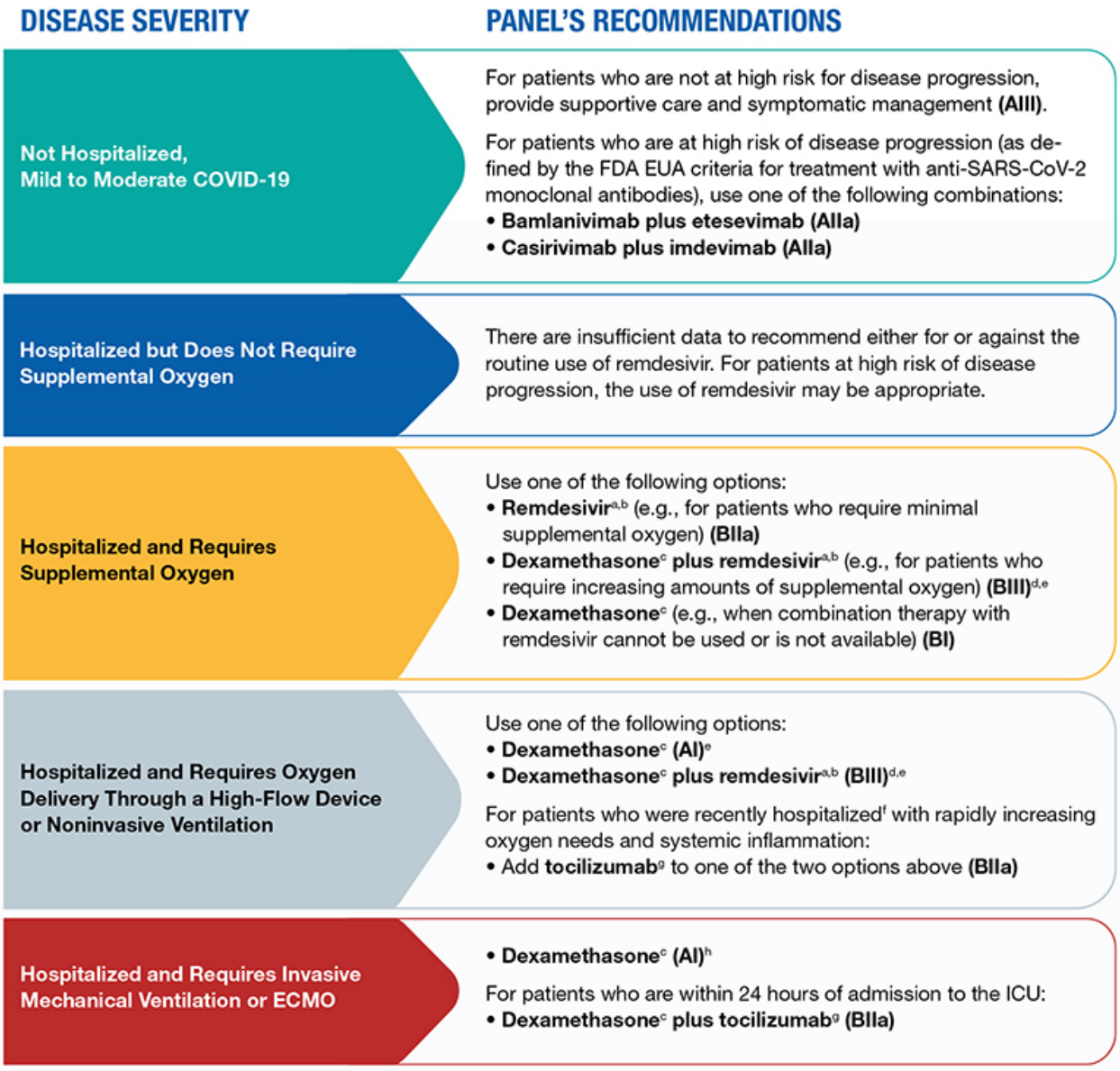
Sotrovimab is a recombinant human IgG1κ monoclonal antibody that binds to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2. Sotrovimab does not compete with human ACE2 receptor binding. This monoclonal antibody is administered intravenously as a one-time infusion of 500 mg.

- There is currently a lack of data to compare the treatment options as it pertains to clinical efficacy and safety.
- Furthermore, the treatment options should not be considered standard of care for the treatment of patients with COVID-19; healthcare providers are encouraged to use clinical judgment regarding best management of COVID-19 positive patients, on a case-by-case basis.
- Unless there is another indication for use of these agents or use is part of a clinical trial, it is not recommended for patients hospitalized because of COVID-19 to receive the above monoclonal antibody treatments.

The National Institutes of Health (NIH)'s COVID-19 Treatment Guidelines Panel reviews the most recent clinical data to provide up-to-date treatment recommendations for clinicians who are caring for patients with COVID-19. The figure below summarizes the panel's recommendations for managing patients with varying severities of disease. Note: it does not yet reflect the addition of sotrovimab to the options for monoclonal antibody treatment.

Figure 1. Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

Doses and durations are listed in the footnotes.



Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

[a] The remdesivir dose is 200 mg IV for one dose, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge (unless the patient is in a health care setting that can provide acute care that is similar to inpatient hospital care). Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.

[b] For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO, remdesivir should be continued until the treatment course is completed.

[c] The dexamethasone dose is 6 mg IV or PO once daily for 10 days or until hospital discharge. If dexamethasone is not available, equivalent doses of other corticosteroids (e.g., prednisone, methylprednisolone, hydrocortisone) may be used. See the Corticosteroids section for more information.

[d] The combination of dexamethasone and remdesivir has not been studied in clinical trials.

[e] In the rare circumstances where corticosteroids cannot be used, **baricitinib plus remdesivir** can be used **(BIIa)**. The FDA has issued an EUA for baricitinib use in combination with remdesivir. The dose for baricitinib is 4 mg PO once daily for 14 days or until hospital discharge.

[f] For example, within 3 days of hospital admission. See the Interleukin-6 Inhibitors section for more information.

[g] The tocilizumab dose is 8 mg/kg of actual body weight (up to 800 mg) administered as a single IV dose. Tocilizumab should not be combined with baricitinib and should be avoided in certain groups of patients who are at increased risk for complications. See the Interleukin-6 Inhibitors section for more information.

[h] The combination of **dexamethasone plus remdesivir** may be considered for patients who have recently been intubated **(CIII)**. The Panel **recommends against** the use of remdesivir monotherapy in these patients.

Key: ECMO = extracorporeal membrane oxygenation; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; ICU = intensive care unit; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally

If you have questions about this guidance, please call your local health department or **1-877-PA-HEALTH** (**1-877-724-3258**).

Clinicians with questions about approved treatments and those with EUAs issued by the FDA should refer to the reference NIH web page: Therapeutic Management | COVID-19 Treatment Guidelines (https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/).

Note: update to the FDA EUA for bamlanivimab: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-monoclonal-antibody-bamlanivimab

Individuals interested in receiving further PA-HANs are encouraged to register at https://www.health.pa.gov/topics/prep/PA-HAN/Pages/HAN.aspx.

Categories of Health Alert messages:
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This information is current as of June 3, 2021 but may be modified in the future. We will continue to post updated information regarding the most common questions about this subject.