Health Advisory:

Updated Guidelines for the Anti-SARS-CoV-2 Monoclonal Antibody Treatment of COVID-19

April 13, 2021

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SUBJECT: **Updated Guidelines for the Anti-SARS-CoV-2 Monoclonal Antibody Treatment of COVID-19**

SARS-CoV-2, virus causing coronavirus disease 2019 (COVID 19), has been evolving over time, resulting in genetic variation in the population of circulating viruses across the world, including the United States. Some of those variations in viral genome can cause resistance to one or more of the monoclonal antibodies (mAb) therapies authorized to treat COVID-19. The ongoing surveillance of human and sewage samples by the Missouri Department of Health and Senior Services (DHSS) indicates rise in variant SARS-CoV-2 in Missouri, similar to other states. This DHSS Health Advisory urges health care providers in Missouri to follow newly updated COVID-19 mAB treatment guidelines issued by the National Institute of Health (NIH).

According to the DHSS surveillance of variant viruses, many of the noted variants including 159 cases of B.1.1.7 (UK origin); 4 cases of B.1.427/B.1.429 (California origin) and 1 case each of B.1.351 (South African origin) and B.1.526 (New York origin) have been identified in Missouri. During the four-week period ending March 13, 2021, the Centers for Disease Control and Prevention (CDC) reports 7.4% of clinical specimens sequenced from Missouri for surveillance purposes were the B.1.1.7, 6.0% were the B.1.427/B.1.429, and 0.2% were B.1.351 variants. As observed in other states, the number and proportion of B.1.1.7 cases in Missouri continues to increase. DHSS has also conducted surveillance through testing community wastewater, which is yielding informative results. Recent sewershed analysis showed that 16 of 18 locations with sufficient genetic material for testing have likely presence of B.1.1.7, 2 of 18 having B.1.427/B.1.429, and only 2 locations having no known variant of concern detected. Although sequencing of SARS-CoV-2 genome from the sewage is a new science, it is showing promising results in being able to provide an early indication of mutations of concern.

Anti-SARS-CoV-2 monoclonal antibodies target SARS-CoV-2 spike protein and block virus entry into cells. Emergency Use Authorization (EUA) 90 initially authorized emergency use of **bamlanivimab** (*Eli Lilly*) alone for the treatment of mild to moderate coronavirus disease 2019 (COVID19) in adults and pediatric patients (12 years of age and older 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 and/or hospitalization. Due to the increase in circulating viral variants in the United States, the FDA requested that manufacture conduct cell culture neutralization studies to assess the activity of **bamlanivimab** against these variants, and/or amino acid substitutions found in these variants. *Eli Lilly* provided pseudovirus data for spike protein substitutions found in variants B.1.1.7 (UK origin), B.1.351 (South Africa origin), P.1 (Brazil origin), B.1.427/B.1.429 (California origin), and B.1.526 (New York origin). Obtained data indicates major reductions in susceptibility for all of the variants studied, except for the one originating in the UK (Table 1).

Table 1. Pseudovirus Neutralization Data for SARS-CoV-2 Variant Substitutions with Bamlanivimab Alone[1]

Lineage with Spike Protein Substitution	Key Substitutions Tested[a]	Fold Reduction in Susceptibility
B.1.1.7 (UK origin)	N501Y	no change[b]
B.1.351 (South Africa origin)	E484K	>2,360[c]
P.1 (Brazil origin)	E484K	>2,360[c]
B.1.427/B.1.429 (California origin)	L452R	>1,020[c]
B.1.526 (New York origin)[d]	E484K	>2,360[c]

[a] For variants with more than one substitution of concern, only the one with the greatest impact on activity is listed.

[b] No change: <5-fold reduction in susceptibility.

[c] No activity was observed at the highest concentration tested. **Bamlanivimab** alone is unlikely to be active against variants from this lineage.

[d] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

For *Eli Lilly's* combination therapy of **bamlanivimab** and **etesevimab**, the treatment fared better against all of the variants than **bamlanivimab** alone (Table 2).

Table 2. Pseudovirus Neutralization Data for SARS-CoV-2 Variant Substitutions with Bamlanivimab and Etesevimab Together[2]

Lineage with Spike Protein Substitution	Key Substitutions Tested[a]	Fold Reduction in Susceptibility
B.1.1.7 (UK origin)	N501Y	no change[b]
B.1.351 (South Africa origin)	K417N + E484K + N501Y	>45[c]
P.1 (Brazil origin)	K417T + E484K + N501Y	>511[c]
B.1.427/B.1.429 (California origin)	L452R	7.4
B.1.526 (New York origin)[d]	E484K	17

[a] For variants with more than one substitution of concern, only the one(s) with the greatest impact on activity is(are) listed.

[b] No change: <5-fold reduction in susceptibility.

[c] No activity was observed at the highest concentration tested. **Bamlanivimab** and **etesevimab** together are unlikely to be active against variants from this lineage.

[d] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

According to the FDA comment, given the similarities between the substitutions in B.1.351 and P.1, it is unlikely that **bamlanivimab** and **etesevimab** together will be active against these variants. *Regeneron's* mAb combination of **casirivimab** with **imdevimab** showed the least reduction in susceptibility against the variants (Table 3).

Table 3. Pseudovirus Neutralization Data for SARS-CoV-2 Variant Substitutions with Casirivimab and Imdevimab Together[3]

Lineage with Spike Protein Substitution	Key Substitutions Tested	Fold Reduction in Susceptibility
B.1.1.7 (UK origin)	N501Y[a]	no change[c]
B.1.351 (South Africa origin)	K417N + E484K + N501Y[b]	no change[c]
P.1 (Brazil origin)	K417T + E484K	no change[c]
B.1.427/B.1.429 (California origin)	L452R	no change[c]
B.1.526 (New York origin)[d]	E484K	no change[c]

[a] Pseudovirus expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: del69-70, del145, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H.

[b] Pseudovirus expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: D80Y, D215Y, del241-243, K417N, E484K, N501Y, D614G, A701V.

[c] No change: <2-fold reduction is susceptibility.

[d] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021)

At this time, it is not known how pseudovirus data correlate with clinical outcomes.

Based on findings described above and other additional information, the NIH has recently updated mAB treatment guidelines for COVID-19 (https://www.covid19treatmentguidelines.nih.gov/statement-on-anti-sars-cov-2-monoclonal-antibodies-eua/), and currently recommends:

- Using one of the following combination anti-SARS-CoV-2 monoclonal antibodies to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression:
  - **Bamlanivimab 700 mg plus etesevimab 1,400 mg**; *or*
  - **Casirivimab 1,200 mg plus imdevimab 1,200 mg**.
- There are no comparative data to determine whether there are differences in clinical efficacy or safety between **bamlanivimab** plus **etesevimab** and **casirivimab** plus **imdevimab.**
  - There are SARS-CoV-2 variants, particularly those that contain the mutation E484K, that reduce the virus' susceptibility to **bamlanivimab** and, to a lesser extent, **casirivimab and etesevimab** in vitro; however, the **clinical impact of these mutations is not known.**
  - In regions where SARS-CoV-2 variants with reduced in vitro susceptibility to **bamlanivimab plus etesevimab** are common, some NIH Panel members would preferentially use **casirivimab** plus **imdevimab** while acknowledging that it is not known whether in vitro susceptibility data correlate with clinical outcomes.
- Because clinical outcome data are limited and there are concerns regarding decreased susceptibility of variants, the Panel **recommends against** the use of **bamlanivimab monotherapy**.
  - If combination products are not available, the use of **bamlanivimab** monotherapy can be considered for people who meet the EUA criteria on a case-by-case basis.

Missouri healthcare providers and public health practitioners: Please contact your local public health agency or the Missouri Department of Health and Senior Services' (DHSS') Bureau of Communicable Disease Control and Prevention at 573-751-6113 or 800-392-0272 (24/7) with questions regarding this Alert. For information on requesting SARS-CoV-2 variant testing in Missouri, please see the DHSS Health Update "Enhancing Public Health Surveillance for Variant SARSCoV-2 Viruses in Missouri" available at https://health.mo.gov/emergencies/ert/alertsadvisories/pdf/update21921.pdf. For additional information on sewershed testing, please contact the Bureau of Environmental Epidemiology at (573) 751-6102 or visit our sewershed storymap at https://storymaps.arcgis.com/stories/f7f5492486114da6b5d6fdc07f81aacf.

References:

1. https://www.fda.gov/media/143603/download?utm_medium=email&utm_source=govdelivery
2. https://www.fda.gov/media/145802/download?utm_medium=email&utm_source=govdelivery
3. Fact Sheet For Health Care Providers Emergency Use Authorization (Eua) Of Regen Covtm (Casirivimab With Imdevimab) (fda.gov)