Drug and Biologic Coverage Policy

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COVID-19 Drug and Biologic Therapeutics

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Related Coverage Resources

Anakinra - (IP0243)
Clinical Trials - (A003)
COVID-19: In Vitro Diagnostic Testing - (0557)
Baricitinib - (IP0225)
Infliximab - (M0003)
Immune Globulins Therapy - (5026)
Immunomodulators - Oral and Subcutaneous (Cigna Total Savings Drug List) - (2102)
Immunomodulators - Oral and Subcutaneous (Individual and Family Plans) - (1903)
Immunomodulators - Oral and Subcutaneous (Standard/Performance, Value/Advantage, Legacy Drug List Plans) - (1805)
Ivermectin - (IP0300)
Tocilizumab Intravenous - (M0004)
Tofacitinib - (IP0230)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses Drugs or Biologics for the treatment, prevention, or management of Coronavirus Disease 2019 (COVID-19) and related symptoms.

Agents addressed in this policy include:
- Anakinra (Kineret®)
- Bamlanivimab and Etesevimab
- Baricitinib (Olumiant®)
- Bebtelovimab

- Casirivimab and Imdevimab (REGEN-COV™)
- Infliximab
- Intravenous Immunoglobulin (IVIG)
- Molnupiravir (Lagevrio™)
- Nirmatrelvir and Ritonavir (Paxlovid™)
- Regiocit
- Remdesivir (Veklury®)
- Sarilumab (Kevzara®)
- Sotrovimab
- Tixagevimab and Cilgavimab (Evusheld™)
- Tocilizumab intravenous (Actemra IV®) EUA / Non-EUA
- Tofacitinib (Xeljanz®/Xeljanz XR®)

The use of anakinra for non-COVID-19 uses is addressed in separate coverage policies. Please refer to the related coverage policy links above (Anakinra, Immunomodulators).

The use of baricitinib for non-COVID-19 uses is addressed in a separate coverage policy. Please refer to the related coverage policy link above (Baricitinib).

The use of infliximab for non-COVID-19 uses is addressed in a separate coverage policy. Please refer to the related coverage policy link above (Infliximab).

The use of immune globulins for non-COVID-19 uses is addressed in a separate coverage policy. Please refer to the related coverage policy link above (Immune Globulins Therapy).

The use of intravenous tocilizumab for non-COVID-19 uses is addressed in a separate coverage policy. Please refer to the related coverage policy link above (Tocilizumab Intravenous).

The use of ivermectin in the management of COVID-19, as well as other conditions, is addressed in a separate coverage policy. Please refer to the related coverage policy link above (Ivermectin).

The use of tofacitinib for non-COVID-19 uses is addressed in a separate coverage policy. Please refer to the related coverage policy link above (Tofacitinib).

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity

The following Drugs or Biologics are considered medically necessary for the treatment, prevention, or management of COVID-19 and related symptoms when EITHER of the following criteria are met:

1. **Drug or Biologic has received a FDA Emergency Use Authorization (EUA) for the treatment of COVID-19, and is used in accordance with the specifications of the EUA**:

Product	Medical Necessity Criteria
Bamlanivimab and Etesevimab **[**As of **1/24/2022,** the Centers for Disease Control and Prevention (CDC) estimated the proportion of COVID-19 cases caused by the	**EITHER** of the following: **1. Treatment, COVID-19. ALL** of the following are met: A. Treatment of mild to moderate COVID-19 in adults and pediatric individuals, including neonates, with positive results of direct SARS-CoV-2 viral testing (for example, molecular [PCR], or antigen [ELISA] laboratory methods) B. **EITHER** of the following: i. Individual is at high risk for progressing to severe COVID-19 and/or hospitalization

Product	Medical Necessity Criteria
Omicron variant to be above 50% in all U.S. Department of Health and Human Services (HHS) regions. **Due to these data, use of Bamlanivimab and Etesevimab is <u>NOT</u> authorized in any U.S. state or territory at this time.** Accordingly and effective immediately, Assistant Secretary for Preparedness & Response (ASPR) has paused sotrovimab distribution to all U.S. states and territories. The FDA has updated the Fact Sheet for sotrovimab to reflect product use restrictions.**]**	ii. Young children (i.e., birth to 2 years of age) who are hospitalized C. Etesevimab may only be administered together with bamlanivimab D. Bamlanivimab and etesevimab are authorized for use <u>only</u> in states, territories, and U.S. jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab administered together is less than or equal to 5%, as determined by FDA *A list of states, territories and U.S. jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized is available on FDA's website at: https://www.fda.gov/media/151719/download* E. Bamlanivimab and etesevimab may only be administered together in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary. F. The use of bamlanivimab and etesevimab covered by this authorization must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets **2. Post-Exposure Prophylaxis, COVID-19. ALL** of the following are met: A. Individual is at high risk for progression to severe COVID-19 B. **EITHER** of the following: i. Individual is <u>not</u> fully vaccinated *Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson's Janssen vaccine)* ii. Individual is not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications) C. **EITHER** of the following: i. Individual has been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC) *Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example).* ii. Individual is at high risk of exposure to an individual infected with SARS-CoV-2 in the same institutional setting (for example, nursing homes, prisons) D. Bamlanivimab and etesevimab may only be administered together E. Bamlanivimab and etesevimab are authorized for use only in states, territories, and U.S. jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab administered together is less than or equal to 5%, as determined by FDA.

Product	Medical Necessity Criteria
	A list of states, territories and U.S. jurisdictions in which bamlanivimab and etesevimab are and are not14 currently authorized is available on FDA's website at: https://www.fda.gov/media/151719/download F. Bamlanivimab and etesevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary G. The use of bamlanivimab and etesevimab covered by this authorization must be in accordance with the authorized Fact Sheets <u>*High Risk*</u> *The following medical conditions or other factors may place adults and pediatric patients (12 to 17 years of age weighing at least 40 kg) at higher risk for progression to severe COVID-19:* • *Older age (for example ≥ 65 years of age)* • *1 year of age or younger* • *Obesity or being overweight (for example, adults with BMI >25 kg/m2, or if 12 to 17 years of age, have BMI ≥ 85th percentile for their age and gender based on CDC growth charts, https://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])* • *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 sotrovimab under the EUA is not limited to the medical conditions or factors listed above.* o *For additional information on medical conditions and factors associated with increased risk for progression to severe COVID, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html* **Bamlanivimab and Etesevimab are <u>NOT</u> authorized by this EUA for use in the following:** A. For treatment of mild to moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency. ***As of <u>1/24/2022</u>, the use of Bamlanivimab and Etesevimab is <u>NOT</u> authorized in any U.S. state or territory at this time due to circulating variant non-susceptibility****. FDA's determination and any updates will be*

Product	Medical Necessity Criteria
	available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs B. In patients 2 years of age and older who are hospitalized due to COVID-19 C. Adults or pediatric patients (regardless of age) who require oxygen therapy due to COVID-19 D. Adults or pediatric patients (regardless of age) who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity E. As a substitute for vaccination against COVID-19 F. Pre-exposure prophylaxis for prevention of COVID-19
Bebtelovimab	**ALL** of the following are met: A. Treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing (for example, molecular [PCR], or antigen [ELISA] laboratory methods) B. Individual is 12 years of age and older, weighing at least 40 kg C. Individual is at high risk† for progressing to severe COVID-19 D. Alternative COVID-19 treatment options approved or authorized by the FDA are not accessible or clinically appropriate (for example, Paxlovid) E. The use of bebtelovimab covered by this authorization must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets <u>*High Risk*</u> *The following medical conditions or other factors may place adults and pediatric patients (12 to 17 years of age weighing at least 40 kg) at higher risk for progression to severe COVID-19:* • *Older age (for example ≥65 years of age)* • *Obesity or being overweight (for example, adults with BMI >25 kg/m2, or if 12 to 17 years of age, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://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])* • *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 sotrovimab under the EUA is not limited to the medical conditions or factors listed above.* o *For additional information on medical conditions and factors associated with increased risk for progression to severe COVID, see the CDC website:*

Product	Medical Necessity Criteria
	*https://www.cdc.gov/coronavirus/2019-ncov/*need-extra-precautions/people-with-medical-conditions.html **Bebtelovimab is <u>NOT</u> authorized by this EUA for use in the following:** A. Adults or pediatric patients who are hospitalized due to COVID-19 B. Adults or pediatric patients who require oxygen therapy and/or respiratory support due to COVID-19 C. Adults or pediatric patients who require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 in those patients on chronic oxygen therapy and/or oxygen support due to underlying non-COVID-19-related comorbidity D. For treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant, based on available information including variant susceptibility to these drugs and regional variant frequency *<u>Note</u>: FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility (see e.g., section 12.4 of authorized Fact Sheet for Health Care Providers), and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions. FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legalregulatory-and-policy-framework/emergency-use authorization#coviddrugs.*
Casirivimab and Imdevimab (REGEN-COV) **[**As of **<u>1/24/2022</u>,** the Centers for Disease Control and Prevention (CDC) estimated the proportion of COVID-19 cases caused by the Omicron variant to be above 50% in all U.S. Department of Health and Human Services (HHS) regions. **Due to these data, use of REGEN-COV is <u>NOT</u> authorized in any U.S. state or territory at this time.** Accordingly and effective immediately, Assistant Secretary for Preparedness & Response (ASPR) has paused sotrovimab distribution to all U.S. states and territories.	**EITHER** of the following: **1. Treatment, COVID-19. ALL** of the following are met: A. Treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing (for example, molecular [PCR], or antigen [ELISA] laboratory methods) B. Individual is 12 years of age and older, weighing at least 40 kg C. Individual is at high risk† for progressing to severe COVID-19 D. Casirivimab and imdevimab may only be administered together E. Casirivimab and imdevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary F. The use of casirivimab and imdevimab covered by this authorization must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets **2. Post-Exposure Prophylaxis, COVID-19. ALL** of the following are met: A. Individual is 12 years of age and older, weighing at least 40 kg B. Individual is at high risk for progression to severe COVID-19 C. **EITHER** of the following: i. Individual is <u>not</u> fully vaccinated *Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson's Janssen vaccine)*

Product	Medical Necessity Criteria
The FDA has updated the Fact Sheet for sotrovimab to reflect product use restrictions.**]**	ii. Individual is not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications) D. **EITHER** of the following: i. Individual has been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC) *Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example).* ii. Individual is at high risk of exposure to an individual infected with SARS-CoV-2 in the same institutional setting (for example, nursing homes, prisons) E. Casirivimab and imdevimab may only be administered together F. Casirivimab and imdevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary G. The use of casirivimab and imdevimab covered by this authorization must be in accordance with the authorized Fact Sheets <u>*High Risk*</u> *The following medical conditions or other factors may place adults and pediatric patients (12 to 17 years of age weighing at least 40 kg) at higher risk for progression to severe COVID-19:* • *Older age (for example ≥65 years of age)* • *Obesity or being overweight (for example, adults with BMI >25 kg/m2, or if 12 to 17 years of age, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://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])* • *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*

Product	Medical Necessity Criteria
	authorization of sotrovimab under the EUA is not limited to the medical conditions or factors listed above: o *For additional information on medical conditions and factors associated with increased risk for progression to severe COVID, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html* **Casirivimab and imdevimab is <u>NOT</u> authorized by this EUA for use in the following:** A. For treatment of mild to moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency. ***As of <u>1/24/2022</u>, the use of REGEN-COV is <u>NOT</u> authorized in any U.S. state or territory at this time due to circulating variant non-susceptibility.*** *FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs* B. Adults or pediatric patients who are hospitalized due to COVID-19 C. Adults or pediatric patients who require oxygen therapy due to COVID-19 D. Adults or pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity E. As a substitute for vaccination against COVID-19 F. Pre-exposure prophylaxis for prevention of COVID-19
Molnupiravir (Lagevrio™)	**EITHER of the following:** A. **ALL** of the following are met: i. Treatment of mild to moderate COVID-19 with positive results of direct SARS-CoV-2 viral testing (for example, molecular [PCR], or antigen [ELISA] laboratory methods) ii. Individual is 18 years of age or older iii. Individual is at high risk for progressing to severe COVID-19 iv. Alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate (for example, bebtelovimab, Paxlovid) v. Molnupiravir covered by this authorization must be in accordance with the authorized Fact Sheets B. Individual has <u>previously</u> received molnupiravir, then **ALL** of the following: i. Individual is experiencing a repeat diagnosis of COVID-19 with positive results of direct SARS-CoV-2 viral testing (for example, molecular [PCR], or antigen [ELISA] laboratory methods) *This is a second diagnosis unrelated to the initial diagnosis of COVID-19 treated with molnupiravir.* ii. At least 120 days have elapsed since completion of the initial course of molnupiravir for treatment of COVID-19 iii. Individual is at high risk† for progressing to severe COVID-19 iv. Alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate (for example, Bamlanivimab-Etesevimab, Paxlovid, REGEN-COV, or Sotrovimab)

Product	Medical Necessity Criteria
	v. Molnupiravir will be in accordance with the authorized Fact Sheets *<u>High Risk</u>* *The following medical conditions or other factors may place adults and pediatric patients (12 to 17 years of age weighing at least 40 kg) at higher risk for progression to severe COVID-19:* • *Older age (for example ≥65 years of age)* • *Obesity or being overweight (for example, adults with BMI >25 kg/m2, or if 12 to 17 years of age, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)* • *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])* • *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 molnupiravir under the EUA is not limited to the medical conditions or factors listed above* **Molnupiravir is <u>NOT</u> authorized by this EUA for use in the following:** A. Individuals < 18 years of age B. Initiation of treatment in patients requiring hospitalization due to COVID-19 *Individual requiring hospitalization due to severe or critical COVID-19 after starting treatment with Paxlovid may complete the full 5-day treatment course per the healthcare provider's discretion.* C. Pre-Exposure or Post-Exposure Prophylaxis for prevention of COVID-19 D. For use longer than 5 consecutive days **Authorization is for one course of treatment (40 capsules) for a duration of 5 days.**
Nirmatrelvir and Ritonavir (Paxlovid)	**EITHER** of the following: A. **ALL** of the following are met: i. Treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing (for example, molecular [PCR], or antigen [ELISA] laboratory methods) ii. Individual is 12 years of age and older, weighing at least 40 kg iii. Individual is at high risk for progressing to severe COVID-19 iv. The use of Paxlovid covered by this authorization must be in accordance with the authorized Fact Sheets. B. Individual has <u>previously</u> received Paxlovid, then **ALL** of the following:

Product	Medical Necessity Criteria
	i. Individual is experiencing a repeat diagnosis of COVID-19 with positive results of direct SARS-CoV-2 viral testing (for example, molecular [PCR], or antigen [ELISA] laboratory methods) *This is a second diagnosis unrelated to the initial diagnosis of COVID-19 treated with Paxlovid.* ii. At least 120 days have elapsed since completion of the initial course of Paxlovid for treatment of COVID-19 iii. Individual is at high risk† for progressing to severe COVID-19 iv. The use of Paxlovid must be in accordance with the authorized Fact Sheets. <u>*High Risk*</u> *The following medical conditions or other factors may place adults and pediatric patients (12 to 17 years of age weighing at least 40 kg) at higher risk for progression to severe COVID-19:* • *Older age (for example ≥65 years of age)* • *Obesity or being overweight (for example, adults with BMI >25 kg/m2, or if 12 to 17 years of age, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://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])* • *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 Paxlovid under the EUA is not limited to the medical conditions or factors listed above* **Paxlovid is <u>NOT</u> authorized by this EUA for use in the following:** A. Initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19 *Individual requiring hospitalization due to severe or critical COVID-19 after starting treatment with Paxlovid may complete the full 5-day treatment course per the healthcare provider's discretion.* B. Pre-Exposure or Post-Exposure Prophylaxis for prevention of COVID-19 C. For use for longer than 5 consecutive days. **Authorization is for one course of treatment (30 tablets/1 carton of 5 blister cards) for a duration of 5 days.**

Product	Medical Necessity Criteria
Regiocit	**ALL** of the following are met: A. Regiocit will be used as a replacement solution only in adult patients being treated with Continuous Renal Replacement Therapy (CRRT) and for whom regional citrate anticoagulation (RCA) is appropriate B. Regiocit will be administered only by a licensed healthcare provider in a critical care setting
Sotrovimab **[**As of **4/5/2022,** the Centers for Disease Control and Prevention (CDC) estimated the proportion of COVID-19 cases caused by the Omicron BA.2 variant to be above 50% in all U.S. Department of Health and Human Services (HHS) regions. **Due to these data, use of sotrovimab is NOT authorized in any U.S. state or territory at this time.** Accordingly and effective immediately, Assistant Secretary for Preparedness & Response (ASPR) has paused sotrovimab distribution to all U.S. states and territories. The FDA has updated the Fact Sheet for sotrovimab to reflect product use restrictions.**]**	**ALL** of the following are met: A. Treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing (for example, molecular [PCR], or antigen [ELISA] laboratory methods) B. Individual is 12 years of age and older, weighing at least 40 kg C. Individual is at high risk for progressing to severe COVID-19 D. Sotrovimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary. E. The use of sotrovimab covered by this authorization must be in accordance with the authorized Fact Sheets. *High Risk* *The following medical conditions or other factors may place adults and pediatric patients (12 to 17 years of age weighing at least 40 kg) at higher risk for progression to severe COVID-19:* • *Older age (for example ≥65 years of age)* • *Obesity or being overweight (for example, adults with BMI >25 kg/m2, or if 12 to 17 years of age, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://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])* • *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 sotrovimab under the EUA is not limited to the medical conditions or factors listed above.* **Sotrovimab is NOT authorized by this EUA for use in the following:** A. Sotrovimab is not authorized for treatment of mild to moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant, based on available information including variant susceptibility to this drug and regional variant frequency

Product	Medical Necessity Criteria
	As of 4/5/2022, the use of Sotrovimab is NOT authorized in any U.S. state or territory at this time due to circulating variant non-susceptibility. *FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs* B. Adults or pediatric patients who are hospitalized due to COVID-19 C. Adults or pediatric patients who require oxygen therapy due to COVID-19 D. Adults or pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity
Tixagevimab and Cilgavimab (Evusheld™)	1. **Pre-Exposure Prophylaxis, COVID-19. ALL** of the following are met: A. Individual is 12 years of age and older, and weighing at least 40 kg B. Individual has not had a known recent exposure to an individual infected with SARS-CoV-2 C. **EITHER** of the following: i. Individual has moderate to severe immune compromise due to a medical condition, or is receiving immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination* ii. Individual 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 (for example, severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s) *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 2 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 <200/mm^3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)* • *Active treatment with high-dose corticosteroids (i.e. ≥ 20 mg prednisone or equivalent per day when administered for ≥ 2 weeks), 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)* **Evusheld is NOT authorized by this EUA for use in the following:** A. For the treatment of COVID-19 B. For Post-Exposure Prophylaxis C. As a substitute for vaccination against COVID-19 in individuals for whom COVID-19 vaccination is recommended

Product	Medical Necessity Criteria
	Individuals for whom COVID-19 vaccination is recommended, including individuals with moderate to severe immune compromise who may derive benefit from COVID-19 vaccination, should receive COVID-19 vaccination.
Tocilizumab intravenous (Actemra IV®)	**ALL** the following are met: A. Treatment of COVID-19 in hospitalized adults and pediatric patients 2 years of age and older B. Individual is receiving systemic corticosteroids C. Individual requires supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO D. Administered only via intravenous infusion E. The use of Actemra covered by this authorization must be in accordance with the authorized Fact Sheets

2. The following product-specific criteria are met:

Product	Medical Necessity Criteria
Anakinra (Kineret®)	**Refractory Multisystem Inflammatory Syndrome in Children (MIS-C). ALL** of the following are met: A. Individual less than 21 years of age B. **EITHER** of the following: i. Positive for current or recent SARS-CoV-2 infection by molecular [PCR], antigen [ELISA] laboratory methods), or serology results ii. COVID-19 exposure within the 4 weeks prior to onset of symptoms C. Individual continues to display the following symptoms and laboratory findings despite intravenous immunoglobulin (IVIG) and glucocorticoid therapy: i. Fever (> 100.4°F for ≥24 hours, or report of subjective fever lasting ≥ 24 hours) ii. Laboratory evidence of inflammation Note: Including, but not limited to, **one** or more of the following: elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, D-dimer, ferritin, lactate dehydrogenase (LDH), interleukin-6 (IL-6), or neutrophils, or reduced lymphocytes or albumin levels. iii. Evidence of clinically severe illness that requires hospitalization with multisystem (i.e., > 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological) D. Other causes have been excluded E. Anakinra will not be used in combination with infliximab Dosing: 5 - 10 mg/kg intravenous (IV) or subcutaneous (SC) in 1 to 4 divided doses administered daily **up to 2 weeks**.
Baricitinib (Olumiant®)	**ALL** of the following are met: A. Treatment of suspected or laboratory confirmed COVID-19 in individuals 2 years of age or older B. Used in hospitalized individuals requiring supplemental oxygen, invasive mechanical ventilation, or ECMO C. Use is for maximum of 14 days or until discharge from the hospital, whichever comes first *Baricitinib may be administered with or without remdesivir.*

Product	Medical Necessity Criteria
Infliximab	**Refractory Multisystem Inflammatory Syndrome in Children (MIS-C). ALL** of the following are met: A. Individual is less than 21 years of age B. **EITHER** of the following: i. Positive for current or recent SARS-CoV-2 infection by molecular [PCR], antigen [ELISA] laboratory methods), or serology results ii. COVID-19 exposure within the 4 weeks prior to onset of symptoms C. Individual continues to display the following symptoms and laboratory findings despite intravenous immunoglobulin (IVIG) and glucocorticoid therapy: i. Fever (> 100.4°F for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours) ii. Laboratory evidence of inflammation *Including, but not limited to, **ONE** or more of the following: elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, D-dimer, ferritin, lactate dehydrogenase (LDH), interleukin-6 (IL-6), or neutrophils, or reduced lymphocytes or albumin levels.* iii. Evidence of clinically severe illness that requires hospitalization with multisystem (i.e., > 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological) D. Other causes have been excluded E. Infliximab will <u>not</u> be used in combination with anakinra <u>Dosing</u>: 5 - 10 mg/kg intravenous (IV) **<u>given one time</u>**.
Intravenous Immunoglobulin (IVIG)	**Multisystem Inflammatory Syndrome in Children (MIS-C). ALL** of the following are met: A. Individual is less than 21 years of age B. Medication is being used for the treatment of Multisystem Inflammatory Syndrome in Children (MIS-C) C. **EITHER** of the following: i. Positive for current or recent SARS-CoV-2 infection by molecular [PCR], antigen [ELISA] laboratory methods), or serology results ii. COVID-19 exposure within the 4 weeks prior to onset of symptoms D. Individual has the following symptoms and laboratory findings: i. Fever (> 100.4°F for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours) ii. Laboratory evidence of inflammation *Including, but not limited to, **ONE** or more of the following: elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, D-dimer, ferritin, lactate dehydrogenase (LDH), interleukin-6 (IL-6), or neutrophils, or reduced lymphocytes or albumin levels.* iii. Evidence of clinically severe illness that requires hospitalization with multisystem (i.e., > 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological) E. Other causes have been excluded F. Intravenous immunoglobulin will be administered in combination with a low-to-moderate glucocorticoid (for example, methylprednisolone 1-2 mg/kg, or equivalent), unless contraindicated or intolerant

Product	Medical Necessity Criteria
	Dosing: 2 g/kg intravenous (up to a maximum total dose of 100 g) **given one time**, or 1 g/kg intravenous per day **times 2 doses** (up to a maximum cumulative dose of 100 g)
Remdesivir (Veklury®)	**EITHER** of the following: A. Hospitalized individuals**, BOTH** of the following are met: i. Used for the treatment of coronavirus disease 2019 (COVID-19) infection ii. Administered via intravenous (IV) infusion B. Non-hospitalized individuals, **ALL** of the following are met: i. Individual weighs 3.5 kg or greater (approximately 7-8 lbs) ii. Mild to moderate COVID-19 who are at high risk of disease progression iii. Administered via intravenous (IV) infusion within 7 days of symptom onset ***Note**: High Risk* *The following medical conditions or other factors may place adults and pediatric patients (12 to 17 years of age weighing at least 40 kg) at higher risk for progression to severe COVID-19:* • *Older age (for example ≥65 years of age)* • *Obesity or being overweight (for example, adults with BMI >25 kg/m2, or if 12 to 17 years of age, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://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])* • *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 sotrovimab under the EUA is not limited to the medical conditions or factors listed above* Dosing**:** • For individuals weighing at least 40 kg (approximately 88 lbs): o Loading dose: 200 mg intravenous (IV) given once on Day 1 of therapy o Maintenance dose: 100 mg IV given once daily beginning on Day 2 • For individuals weighing at least 3 kg and less than 40 kg (approx. 6.6 lbs to 88 lbs): o Loading dose: 5 mg/kg IV given on Day 1 o Maintenance dose: 2.5 mg/kg IV given once daily beginning on Day 2 • Duration of therapy: o For Hospitalized individuals, duration of therapy is up to 10 days

Product	Medical Necessity Criteria
	o For Outpatient treatment of individuals, duration of therapy is up to 3 days
Sarilumab (Kevzara)	**BOTH** of the following: A. Individual has met ALL medical necessity criteria for tocilizumab (Actemra IV®) intravenous B. Documented inability to obtain tocilizumab intravenous
Tocilizumab intravenous (Actemra IV®)	The following is met: A. For the treatment of Cytokine Release Syndrome (CRS) associated with COVID-19
Tofacitinib (Xeljanz/ Xeljanz XR)	**BOTH** of the following: A. Individual has met **ALL** medical necessity criteria for baricitinib (Olumiant®) B. Documented inability to obtain baricitinib

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Conditions Not Covered

Any Drug or Biologic product that does not fall into one of the above categories is considered experimental, investigational or unproven for the treatment, prevention, or management of COVID-19, including the following:

1. **Concurrent use of interleukin-6 blockers** (for example, sarilumab, tocilizumab) **and janus kinase inhibitors** (for example, baricitinib, tofacitinib)
   - The National Institute of Health COVID-19 Treatment Guidelines, and Infectious Diseases Society of America (IDSA) Guidelines on the Treatment and Management of Patients with COVID-19 recommend against the use of baricitinib in combination with tocilizumab or other IL-6 inhibitors for the treatment of COVID-19. As both are potent immunosuppressants, there is the potential for an additive risk of infection. (IDSA, 2021; NIH, 2021)

2. **Concurrent use of molnupiravir and Paxlovid (nirmatrelvir and ritonavir)**
   - There are no data on the use of combination of molnupiravir with Paxlovid. Clinical trials are needed to determine whether combination therapy has a role in the treatment of COVID-19. (NIH, 2021)

Other Uses with Supportive Evidence

Multisystem Inflammatory Syndrome in Children (including refractory disease): Anakinra, Infliximab, Intravenous Immunoglobulin

National Institute of Health (NIH) COVID-19 Treatment Guidelines[37]

Multiple nonrandomized studies suggest that front-line IVIG in combination with glucocorticoids is associated with less treatment failure, faster recovery of cardiac function, shorter intensive care unit (ICU) stay, and decreased requirement for treatment escalation compared to IVIG monotherapy. Based on these data, the Panel recommends using **IVIG** in combination with low-to-moderate-dose **glucocorticoids** for children hospitalized with MIS-C **(AIIb)**. The Panel recommends against the routine use of IVIG monotherapy for the treatment of MIS-C unless glucocorticoid use is contraindicated **(AIIb)**.

IVIG should be given at a dose of 2 g/kg of ideal body weight up to a maximum dose of 100 grams. The patient's cardiac function and fluid status should be monitored carefully during the IVIG infusion. IVIG can be given in divided doses of 1 g/kg of ideal body weight over 2 days if there is a concern about the patient's fluid status. Methylprednisolone 1 to 2 mg/kg/day, or another glucocorticoid at an equivalent dose, is considered low-to-

moderate glucocorticoid dosing. Once there is clinical improvement (i.e., the child is afebrile, end organ dysfunction resolves, and inflammatory markers are trending downward), a steroid taper should be initiated. Typically, the taper lasts for several weeks to avoid rebound inflammation and is guided by the clinical status of the patient.

A second dose of IVIG is not commonly reported in the literature as a strategy for intensification therapy in MIS-C. This may be due to the high rates of IVIG resistance, the rapid pace of disease escalation, and the risk for fluid overload in MIS-C patients. Therefore, the Panel **recommends against** a second dose of **IVIG** for intensification therapy in patients with refractory MIS-C **(BIII)**.

Intensification therapy is recommended for children with refractory MIS-C who do not improve within 24 hours of initial immunomodulatory therapy **(AIII)**. Children with uncontrolled MIS-C despite treatment with IVIG and low-to-moderate-dose glucocorticoids will often continue to deteriorate without further intervention, and this decline in clinical status can be quite rapid. For children with refractory MIS-C, the Panel recommends additional immunomodulatory therapy (in alphabetical order) with **anakinra (BIIb)**, higher-dose **glucocorticoids (BIIb)**, or **infliximab (BIIb)**. High-dose anakinra (5–10 mg/kg/day) is recommended for MIS-C based on the improved efficacy of anakinra used at higher doses for macrophage activation syndrome. The duration of anakinra therapy varies in the literature and is used by some patients for long periods (e.g., up to 2 weeks) as a steroid sparing agent. The Panel recommends a single dose of infliximab 5 to 10 mg/kg IV. Although the half-life of infliximab in MIS-C is unknown, it likely has effects that persist for several weeks. This extended period of drug activity can allow for a steroid-sparing effect in MIS-C. Currently, there is insufficient evidence to determine which of these agents is most effective for intensification therapy in patients with refractory MIS-C. In certain patients with severe illness, intensification therapy may include dual therapy with higher-dose **glucocorticoids** and **anakinra (BIII)** or higher-dose **glucocorticoids** and **infliximab (BIII)**. Anakinra and infliximab **should not be used** in combination.

American College of Rheumatology: Clinical Guidance for Pediatric Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 and Hyperinflammation in COVID-19 [38]

Patients under investigation for MIS-C without life-threatening manifestations should undergo diagnostic evaluation for MIS-C as well as other possible infectious and non-infectious etiologies before immunomodulatory treatment is initiated (M). Patients under investigation for MIS-C with life-threatening manifestations may require immunomodulatory treatment for MIS-C before the full diagnostic evaluation can be completed (H). After evaluation by specialists with expertise in MIS-C, some patients with mild symptoms may require only close monitoring without immunomodulatory treatment (M). The panel noted uncertainty around the empiric use of intravenous immunoglobulin (IVIG) in this setting to prevent coronary artery aneurysms (CAAs).

- A stepwise progression of immunomodulatory therapies should be used to treat MIS-C with **IVIG and low-moderate dose glucocorticoids** considered first tier therapy in most hospitalized patients (M).
- High dose glucocorticoids, **anakinra**, or **infliximab** should be used as intensification therapy in patients with refractory disease (M).
- IVIG
    - High dose **IVIG** (typically 2 gm/kg, based on ideal body weight, max 100gm) should be used for treatment of MIS-C (M).
    - Cardiac function and fluid status should be assessed in MIS-C patients before IVIG treatment is provided. Patients with depressed cardiac function may require close monitoring and diuretics with IVIG administration (H).
    - In some patients with cardiac dysfunction, IVIG may be given as divided doses (1 gm/kg daily over 2 days) (M).
    - Low-moderate dose glucocorticoids (1-2 mg/kg/day) should be given with IVIG as dual therapy for treatment of MIS-C in hospitalized patients (M).
    - In patients with refractory MIS-C despite a single dose of IVIG, **a second dose of IVIG is <u>not</u> recommended** given the risk of volume overload and hemolytic anemia associated with large doses of IVIG (H).

    - In patients who do not respond to IVIG and low-moderate dose glucocorticoids, high dose, IV pulse glucocorticoids (10-30 mg/kg/day) should be considered, especially if a patient requires high dose or multiple inotropes and/or vasopressors (M).
- Refractory MIS-C
    - High dose **anakinra** (>4 mg/kg/day IV or SQ) should be considered for treatment of MIS-C refractory to IVIG and glucocorticoids, in patients with MIS-C and features of macrophage activation syndrome (MAS), or in patients with contraindications to long-term use of glucocorticoids (M).
    - **Infliximab** (5-10 mg/kg/day IV x1 dose) may be considered as an alternative biologic agent to anakinra for treatment of MIS-C refractory to IVIG and glucocorticoids or in patients with contraindications to long-term use of glucocorticoids. Infliximab should not be used to treat patients with MIS-C and features of MAS (M).
- Serial laboratory testing and cardiac assessment should guide immunomodulatory treatment response and tapering. Patients may require a 2-3-week, or even longer, taper of immunomodulatory medications (H).

Remdesivir

National Institute of Health (NIH) COVID-19 Treatment Guidelines

When the Omicron variant represents the majority (e.g., >80%) of infections in a region, it is expected that bamlanivimab plus etesevimab and casirivimab plus imdevimab will not be active for treatment or post-exposure prophylaxis (PEP) of COVID-19. (NIH, 2021)

In this setting, the Panel recommends using 1 of the following options to treat non-hospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression:

- Sotrovimab 500 mg IV as a single infusion (AIIa) administered as soon as possible and within 10 days of symptom onset; or
- **Remdesivir 200 mg IV on Day 1, then 100 mg once daily on Days 2 and 3 (BIIa) initiated as soon as possible and within 7 days of symptom onset.**
    - Because remdesivir requires IV infusion for 3 consecutive days, logistical constraints may make it difficult to administer the drug in some settings
    - Remdesivir should be administered in a setting where management of severe hypersensitivity reactions, such as anaphylaxis, is possible. Patients should be monitored during the infusion and observed for at least 1 hour after the infusion.
    - Remdesivir is currently FDA-approved for hospitalized individuals; however, use of the drug for outpatient treatment would be an off-label indication.

If neither sotrovimab nor remdesivir are feasible to use, and the Delta VOC still represents a significant, but not dominant proportion (e.g., ≥20%) of infections in the region:

- Patients could be offered bamlanivimab plus etesevimab or casirivimab plus imdevimab with the understanding that treatment would be ineffective if they are infected with the Omicron variant.
- Consider the use of bamlanivimab plus etesevimab or casirivimab plus imdevimab for PEP on a case-by-case basis with the understanding that the drugs may be ineffective if the person has been exposed to the Omicron variant.

Infectious Diseases Society of America (IDSA)

- **Among ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel suggests remdesivir initiated within seven days of symptom onset rather than no remdesivir. (Conditional recommendation, Low certainty of evidence) (IDSA, 2021)**

Remarks:

- Dosing for remdesivir is 200 mg on day one followed by 100 mg on days two and three.
- Patients with mild to moderate COVID-19 who are at high risk of progression to severe disease admitted to the hospital for reasons other than COVID-19 may also receive remdesivir
- Options for treatment and management of ambulatory patients include nirmatrelvir/ritonavir, three-day treatment with remdesivir, molnupiravir, and neutralizing monoclonal antibodies. Patient specific factors (e.g.,

symptom duration, renal function, drug interactions), product availability, and institutional capacity and infrastructure should drive decision-making regarding choice of agent. Data for combination treatment do not exist in this setting

Sarilumab (Kevzara)

National Institute of Health (NIH) COVID-19 Treatment Guidelines

- **The Panel recommends sarilumab only when tocilizumab is not available or is not feasible to use (BIIa).** (NIH, 2021)

- Rationale for this recommendation:
    - Even though the REMAP-CAP trial supports that sarilumab and tocilizumab have similar efficacy in the treatment of hospitalized patients with COVID-19, the evidence for the efficacy of tocilizumab is more extensive than that for sarilumab
    - Currently, sarilumab is only approved as a subcutaneous (SQ) injection in the United States.
    - REMAP-CAP trial, the efficacy of tocilizumab and sarilumab in improving survival and reducing duration of organ support was similar. Compared to non-contemporary control patients who received placebo plus dexamethasone, patients who received sarilumab and dexamethasone demonstrated reduced mortality, shorter time to ICU discharge, and more organ support-free days.
        - In this study, sarilumab in combination with dexamethasone (n = 483) was non-inferior to tocilizumab with dexamethasone (n = 943) with regards to the number of organ support-free days and mortality with a probability of 99% and 98%, respectively.
        - In the REMAP-CAP trial, a single dose of sarilumab 400 mg for SQ injection was reconstituted in 50 ml or 100 ml of normal saline and administered as an intravenous infusion over 1 hour.

- Recommended Dosing:
    - Use the single-dose, pre-filled syringe (not the pre-filled pen) for SQ injection. Reconstitute sarilumab 400 mg in 100 cc 0.9% NaCl and administer as an IV infusion over 1 hour
    - In the United States, the currently approved route of administration for sarilumab is SQ injection. In the REMAP-CAP trial, the SQ formulation was used to prepare the IV infusion.

Infectious Diseases Society of America (IDSA)

- **When tocilizumab is not available, for patients who would otherwise qualify for tocilizumab, the IDSA guideline panel suggests sarilumab in addition to standard of care (i.e., steroids) rather than standard of care alone**. (**Conditional recommendation, Very low certainty of evidence)** (IDSA, 2021)

Tocilizumab intravenous (Actemra IV)

In COVID-19, the body may respond to the virus by overproducing immune cells and their signaling molecules in a phenomenon called cytokine release storm. By inhibiting IL-6, Actemra is speculated to be associated with better clinical outcomes, such as decreased systemic inflammation, improved survival rate, better hemodynamic and improved of respiratory distress. Clinical trials are underway evaluating Actemra in patients with severe or critical cytokine release syndrome. (U.S. NIH, 2020)

In a retrospective analysis from China, 21 patients with severe or critical COVID-19 were treated with Actemra IV (18 patients received one dose [400 mg IV] and 3 patients received a second dose within 12 hours). All patients had a 1-week history of routine treatment prior to Actemra. All patients received standard therapy, including lopinavir, methylprednisolone, other symptom relievers, and oxygen therapy. The mean age of enrolled patients was 57 years (range 25 to 88 years), and the majority (n = 18/21) were male. Overall, 17 patients were categorized with severe disease (defined as respiratory rate ≥ 30 breaths/min, peripheral oxygen saturation [SpO2] ≤ 93% [room air], and/or partial pressure of arterial oxygen/percentage of inspired oxygen [PaO2/FiO2] ≤ 300 mmHg). There were also four patients categorized as critical (defined as respiratory failure requiring mechanical ventilation; shock; or intensive care unit admission combined with other organ failure). All patients

had abnormal computed tomography (CT) of the chest, primarily with plaque-like, ground-glass opacities and focal consolidation, mainly distributed in the peripheral (especially the subpleural) region. Mean IL-6 expression levels (132.38 ± 278.54 pg/ml) prior to administration of Actemra suggested upregulation of IL-6. Body temperature of all patients normalized on the first day after receiving Actemra and remained stable thereafter. After treatment, CT scans showed that the chest lesions were absorbed in 19 patients (90.5%). At the time this analysis was published, 19 patients (90.5%) were discharged (average of 13.5 days after the treatment with Actemra) and the remaining patients continued to recover. There have been no reports of subsequent pulmonary infection, deterioration of illness, or death. (Xu, 2020)

Tofacitinib (Xeljanz / Xeljanz XR)

National Institute of Health (NIH) COVID-19 Treatment Guidelines

- **The Panel recommends tofacitinib as an alternative to baricitinib only when baricitinib is not available or not feasible to use (BIIa) because the evidence for the effectiveness of tofacitinib is less extensive than that for baricitinib.** (NIH, 2021)

- Rationale for Recommending the Use of Tofacitinib Plus Dexamethasone in Certain Hospitalized Patients:
    - In the STOP-COVID trial, a double-blind, placebo-controlled randomized trial, use of tofacitinib was associated with a decreased risk of respiratory failure and death (risk ratio 0.63; 95% CI, 0.41–0.97). All-cause mortality within 28 days occurred among 2.8% of the participants in the tofacitinib arm (n = 144) and 5.5% in the placebo arm (n = 145) (HR 0.49; 95% CI, 0.15–1.63). Approximately 80% of participants in each arm also received corticosteroids. Serious adverse events occurred in 14.2% of the participants in the tofacitinib group and in 12.0% in the placebo group.26
    - The STOP-COVID trial supports that tofacitinib plus steroids is effective in improving outcomes in hospitalized patients with COVID-19. Both baricitinib and tofacitinib belong to the same class of anti-inflammatory drugs, the kinase inhibitors, and have overlapping mechanisms of action.

- Recommended Dosing:
    - 10 mg orally twice daily for up to 14 days, or until hospital discharge
    - eGFR less than 60 mL/min/1.73 m^2: tofacitinib 5 mg orally twice daily

Infectious Diseases Society of America (IDSA)

- **Recommendation 21: Among hospitalized adults with severe COVID-19, but not on non-invasive or invasive mechanical ventilation, the IDSA panel suggests tofacitinib rather than no tofacitinib. (Conditional recommendation, Low certainty of evidence)** (IDSA, 2021)

- Tofacitinib has a lower level of certainty of evidence than baricitinib per IDSA:
    - **Recommendation 19: Among hospitalized adults with severe COVID-19 having elevated inflammatory markers, the IDSA panel suggests baricitinib rather than no baricitinib. (Conditional recommendation, Moderate certainty of evidence)**

    - Other Remarks: Patients who receive tofacitinib should not receive tocilizumab or other IL-6 inhibitor for treatment of COVID-19.

Infectious Diseases Society of America Evidence Rating

- High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
- Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
- Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

National Institute of Health Evidence Rating

- Rating of Recommendations: A = Strong; B = Moderate; C = Weak

- 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

American College of Rheumatology Evidence Rating

- A 9-point scale was used to determine the appropriateness of each statement (1-3, inappropriate; 4-6, uncertain; 7-9, appropriate)
- Consensus was rated as low (L), moderate (M), or high (H) based on dispersion of the votes along the numeric scale
- Approved guidance statements had to be classified as appropriate with moderate (M) or high (H) levels of consensus

Health Care Provider Fact Sheet

FDA EUA Fact Sheet

Bamlanivimab *EUA revoked on 4/16/2021	LIMITATIONS OF AUTHORIZED USE Bamlanivimab is 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 Benefit of treatment with bamlanivimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation [see Warnings and Precautions (5.2)]. Patient Selection and Treatment Initiation This section provides essential information on the unapproved product bamlanivimab for the treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization [see Limitations of Authorized Use]. High risk is defined as patients who meet at least ONE of the following criteria: • Have a body mass index (BMI) ≥35 • Have chronic kidney disease • Have diabetes • Have immunosuppressive disease • Are currently receiving immunosuppressive treatment • Are ≥65 years of age • Are ≥55 years of age AND have: o cardiovascular disease, OR o hypertension, OR o chronic obstructive pulmonary disease/other chronic respiratory disease. • Are 12 – 17 years of age AND have: o BMI ≥ 85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm, OR o sickle cell disease, OR o congenital or acquired heart disease, OR o neurodevelopmental disorders, for example, cerebral palsy, OR o a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR

	o asthma, reactive airway or other chronic respiratory disease that requires daily medication for control Dosage • The dosage of bamlanivimab in adults and pediatric patients 12 years of age and older weighing at least 40 kg is a single IV infusion of 700 mg bamlanivimab administered over at least 60 minutes. • **Bamlanivimab should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset.** Bamlanivimab must be administered by **intravenous (IV) infusion**. Dosage Adjustment in Specific Populations No dosage adjustment is recommended based on age, sex, race, body weight, renal or mild hepatic impairment, during pregnancy or while lactating, or for disease severity or inflammation [see Full EUA Prescribing Information, Use in Specific Populations (11)]. Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19 Benefit of treatment with bamlanivimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, bamlanivimab is not authorized for use in patients [see Limitations of Authorized Use]: • 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 Antiviral Resistance There is a potential risk of treatment failure due to the development of viral SARS-CoV-2 variants that are resistant to bamlanivimab. Prescribing healthcare providers should consider the prevalence of bamlanivimab resistance variants in their area, where data are available, when considering treatment options. Evaluation of susceptibility of variants identified through global surveillance and in subjects treated with bamlanivimab is ongoing. Pseudovirus harboring the E484K substitution had reduced susceptibility to bamlanivimab; this substitution is found in several lineages, including B.1.351 (South Africa origin), P.1 (Brazil origin) and B.1.526 (New York origin). In addition, pseudoviruses with the spike protein and concurrent spike substitutions present in the South African B.1.351 origin variant lineage (K417N + E484K + N501Y), and the Brazil origin P.1 variant lineage (K417T + E484K + N501Y) exhibited reduced susceptibility to bamlanivimab. Pseudovirus harboring the L452R and the spike protein from the California origin variant lineage B.1.427/B.1.429 exhibited reduced susceptibility to bamlanivimab. Bamlanivimab retained activity against pseudovirus expressing del69-70 + N501Y spike substitutions found in the UK origin B.1.1.7 variant lineage (Table 3).

Table 3: Pseudovirus Neutralization Data for SARS-CoV-2 Variant Substitutions with Bamlanivimab Alone

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).

It is not known how pseudovirus data correlate with clinical outcomes; however, reduction in susceptibility of >1,000-fold indicates that there will likely be no activity of bamlanivimab alone against these variants.

It is possible that bamlanivimab resistance-associated variants could have cross-resistance to other mAbs targeting the receptor binding domain of SARS-CoV-2. The clinical impact is not known.

Bamlanivimab and Etesevimab

AUTHORIZED USE

TREATMENT

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved products bamlanivimab and etesevimab administered together for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric, including neonates, with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Limitations of Authorized Use

- Bamlanivimab and etesevimab are not authorized for treatment of mild to moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency.
    - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.
- Bamlanivimab and etesevimab are not authorized for use in patients 2 years and older who are hospitalized due to COVID-19.
- Bamlanivimab and etesevimab are not authorized for use in patients, regardless of age, who: o require oxygen therapy and/or respiratory support due to COVID-19, OR o require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 and are on chronic oxygen therapy and/or respiratory support due to underlying non-COVID-19 related comorbidity.
- Treatment with bamlanivimab and etesevimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab and etesevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

POST-EXPOSURE PROPHYLAXIS

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved products

	bamlanivimab and etesevimab administered together in adults and pediatric, including neonates, for post-exposure prophylaxis of COVID-19 in individuals who are at high risk of progression to severe COVID-19, including hospitalization or death, and are: • not fully vaccinated **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications) **and** o have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC) **or** o who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) <u>Limitations of Authorized Use</u> • Bamlanivimab and etesevimab are not authorized for post-exposure prophylaxis of COVID-19 in geographic regions where exposure is likely to have been to a non-susceptible SARS-CoV-2 variant, based on available information including variant susceptibility to these drugs and regional variant frequency. o FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs. • Post-exposure prophylaxis with bamlanivimab and etesevimab is not a substitute for vaccination against COVID-19. • Bamlanivimab and etesevimab are not authorized for pre-exposure prophylaxis for prevention of COVID-19. Bamlanivimab and etesevimab have been authorized by FDA for the emergency uses described above. **Bamlanivimab and etesevimab are <u>not</u> FDA-approved for these uses.** <u>Criteria for Identifying High Risk Individuals</u> The following medical conditions or other factors may place adults and pediatric patients (12 to 17 years of age weighing at least 40 kg) at higher risk for progression to severe COVID-19: • Older age (for example ≥65 years of age) • < 1 year old • Obesity or being overweight (for example, adults with BMI >25 kg/m2, or if 12 to 17 years of age, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://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])

	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 sotrovimab under the EUA is not limited to the medical conditions or factors listed above. o For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: https://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. **PRESCRIBING INFORMATION** **Under this EUA, bamlanivimab and etesevimab must be administered together after dilution as a <u>single</u> <u>intravenous (IV) infusion only</u>.** <u>Treatment Dosage</u> The dosage in adults (18 years and older) and pediatric patients (<18 years and weighing at least 40 kg) is bamlanivimab 700 mg and etesevimab 1,400 mg. The dosage for pediatric patients weighing less than 40 kg will vary depending on body weight: • > 20 kg to <40 kg: 350 mg bamlanivimab and 700 mg etesevimab • >12 kg to 20 kg: 175 mg bamlanivimab and 350 mg etesevimab • 1 kg to 12 kg: 12 mg/kg bamlanivimab and 24 mg/kg etesevimab For treatment of COVID-19, bamlanivimab and etesevimab should be administered together as soon as possible after positive results of direct SARS-CoV-2 viral testing and **within 10 days of symptom onset**. <u>Post-Exposure Prophylaxis Dosage</u> The dosage in adults (18 years and older) and pediatric individuals (<18 years and weighing at least 40 kg) is 700 mg bamlanivimab and 1,400 mg etesevimab administered together as a single intravenous infusion. The dosage for pediatric individuals weighing less than 40 kg will vary depending on body weight: • >20 kg to <40 kg: 350 mg bamlanivimab and 700 mg etesevimab • >12 kg to 20 kg: 175 mg bamlanivimab and 350 mg etesevimab • 1 kg to 12 kg: 12 mg/kg bamlanivimab and 24 mg/kg etesevimab For post-exposure prophylaxis, bamlanivimab and etesevimab should be given together **as soon as possible following exposure to SARS-CoV-2**. <u>Antiviral Resistance</u> There is a potential risk of treatment failure due to the development of viral variants that are resistant to bamlanivimab and/or etesevimab. There are other authorized monoclonal antibody treatments available and healthcare providers should choose an authorized therapeutic option with activity against circulating variants in their state, territory, or US jurisdiction. Please consult the bamlanivimab-etesevimab Fact Sheet For Healthcare Providers for the latest bamlanivimab-etesevimab microbiology/antiviral resistance information.
Baricitinib (Olumiant)	**<u>AUTHORIZED USE</u>** This EUA is for the unapproved use of baricitinib to treat COVID-19 in hospitalized pediatric patients 2 to less than 18 years of age requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. <u>INSTRUCTIONS FOR ADMINISTRATION</u> <u>Pediatric Patients</u>

	• Limited data informing baricitinib dosing in pediatric patients comes from ongoing clinical trials for other uses. Based on the available information, treatment for COVID-19 for pediatric patients under this EUA is as follows: • The recommended dosage for patients 9 years of age and older is 4 mg once daily for 14 days of total treatment or until hospital discharge, whichever is first. • The recommended dosage for patients ages 2 years through less than 9 years of age is 2 mg once daily for 14 days of total treatment or until hospital discharge, whichever is first. • Baricitinib is not authorized for patients younger than 2 years of age • Dosage adjustments in patients with renal or hepatic impairment are recommended Administration Baricitinib tablets are given orally once daily with or without food. Alternate Administration o For patients who are unable to swallow whole tablets, alternate administration may be considered: • Oral dispersion • Gastrostomy tube (G tube) • Nasogastric tube (NG tube)
Bebtelovimab	**AUTHORIZED USE** The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of bebtelovimab for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) 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 risk1 for progression to severe COVID-19, including hospitalization or death, and • for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate Information Regarding Available Alternatives for the EUA Authorized Use Although Veklury is an approved alternative treatment of mild-to-moderate COVID-19 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 progression to severe COVID-19, including hospitalization or death, FDA does not consider Veklury to be an adequate alternative to bebtelovimab for this authorized use because it may not be feasible or practical for certain patients (e.g., it requires a 3-day treatment duration). LIMITATIONS OF AUTHORIZED USE • Bebtelovimab is not authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to this drug and regional variant frequency. o FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs. • Bebtelovimab is not authorized for use in patients, who are hospitalized due to COVID-19, OR o require oxygen therapy and/or respiratory support due to COVID-19, OR o require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 and are on chronic oxygen therapy and/or respiratory support due to underlying non-COVID-19 related comorbidity.

	Treatment with bebtelovimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bebtelovimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation [see Warnings and Precautions (5.3)]. **Bebtelovimab is not FDA-approved for any use, including for use as treatment of COVID-19.** **DOSAGE AND ADMINISTRATION** Dosage • The dosage in adults (18 years and older) and pediatric patients (≥12 years of age and weighing at least 40 kg) is bebtelovimab 175 mg. • Administer bebtelovimab as soon as possible after positive results of direct SARS-CoV-2 viral testing and within **7 days** of symptom onset. • Bebtelovimab must be administered as a single intravenous injection over at least 30 seconds. Administration • Bebtelovimab should be prepared by a qualified healthcare professional using aseptic technique. • Bebtelovimab may only be administered in settings in which healthcare providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary. • **Clinically monitor patients for possible infusion-related reactions during administration and observe patients for at least 1 hour after injection is complete.** **Antiviral Resistance** There is a potential risk of treatment failure due to the development of viral variants that are resistant to bebtelovimab. Refer to the Health Care Provider Fact Sheet for up to date viral resistance information.
Casirivimab and Imdevimab (REGEN-COV)	**AUTHORIZED USE** **1. TREATMENT:** • REGEN-COV (casirivimab and imdevimab) is authorized for use under an Emergency Use Authorization (EUA) for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) 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 progression to severe COVID-19, including hospitalization or death. • Limitations of Authorized Use: o REGEN-COV is not authorized for treatment of mild to moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information such as variant susceptibility to this drug and regional variant frequency. ▪ FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs. o Casirivimab and imdevimab 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
  - Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients requiring high flow oxygen or mechanical ventilation with COVID-19.

2. <u>POST-EXPOSURE PROPHYLAXIS:</u>

- The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk† for progression to severe COVID-19, including hospitalization or death, and are:
  - not fully vaccinated* or who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications) **and**

    <u>Note</u>: individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson's Janssen vaccine)

  - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)** **OR**

    ****<u>Note</u>: Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example).***

  - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons)

- <u>Limitations of Authorized Use:</u>
  - REGEN-COV is not authorized for post-exposure prophylaxis of COVID-19 in geographic regions where exposure is likely to have been to a non-susceptible SARS-CoV-2 variant, based on available information including variant susceptibility to this drug and regional variant frequency.
    - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs
  - Post-exposure prophylaxis with REGEN-COV (casirivimab and imdevimab) is not a substitute for vaccination against COVID-19.
  - REGEN-COV (casirivimab and imdevimab) is not authorized for pre-exposure prophylaxis for prevention of COVID-19.

Casirivimab and imdevimab are <u>not</u> FDA-approved for these uses.

	†**Note**: Criteria for Identifying High Risk Individuals The following medical conditions or other factors may place adults and pediatric patients (12 to 17 years of age weighing at least 40 kg) at higher risk for progression to severe COVID-19: • Older age (for example ≥65 years of age) • Obesity or being overweight (for example, adults with BMI >25 kg/m2, or if 12 to 17 years of age, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://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]) ▪ 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 sotrovimab under the EUA is 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: https://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. Routes of Administration for REGEN-COV: • REGEN-COV may be administered by intravenous infusion or subcutaneous injection • **FOR TREATMENT, INTRAVENOUS INFUSION IS STRONGLY RECOMMENDED. SUBCUTANEOUS INJECTION IS AN ALTERNATIVE ROUTE OF ADMINISTRATION WHEN INTRAVENOUS INFUSION IS NOT FEASIBLE AND WOULD LEAD TO DELAY IN TREATMENT** • **FOR POST-EXPOSURE PROPHYLAXIS, EITHER SUBCUTANEOUS INJECTION OR INTRAVENOUS INFUSION CAN BE USED** Dosage: **Treatment Dosage** • The authorized dosage is 600 mg of casirivimab and 600 mg of imdevimab administered together as a single intravenous infusion or by subcutaneous injection as soon as possible after positive SARS-CoV-2 viral testing and within 10 days of symptom onset [see Dosage and Administration (2.2) and Clinical Trial Results and Supporting Data for EUA (18.1)]. • The authorized dosage of 600 mg of casirivimab and 600 mg of imdevimab for subcutaneous administration for treatment is selected based on the totality of the scientific evidence, incorporating clinical data, viral load reduction data (pharmacodynamics) and pharmacokinetic data [see Clinical Pharmacology (14.2)and (14.3)].

	Post-exposure Prophylaxis Dosage • The authorized dosage is 600 mg of casirivimab and 600 mg of imdevimab administered by subcutaneous injection or together as a single intravenous infusion as soon as possible following exposure to SARS-CoV-2. • For individuals in whom repeat dosing is determined to be appropriate for ongoing exposure to SARS-CoV-2 for longer than 4 weeks and who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination, the initial dose is 600 mg of casirivimab and 600 mg of imdevimab by subcutaneous injection or intravenous infusion followed by subsequent repeat dosing of 300 mg of casirivimab and 300 mg of imdevimab by subcutaneous injection or intravenous infusion once every 4 weeks for the duration of ongoing exposure. • The authorized dosage including dosage for repeat dosing is based on the totality of the scientific evidence including clinical pharmacology data and clinical trial data [see Clinical Trial Results and Supporting Data for EUA (18.2) and Clinical Pharmacology (14.3)] REGEN-COV may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion or hypersensitivity reactions, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary. Antiviral Resistance There is a potential risk of treatment failure due to the development of viral variants that are resistant to casirivimab and imdevimab administered together. Prescribing healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering treatment options. Please consult the REGEN-COV Fact Sheet For Healthcare Providers for the latest REGEN-COV microbiology/antiviral resistance information.
Molnupiravir (Lagevrio)	**AUTHORIZED USE** The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product molnupiravir for treatment of mild-to-moderate COVID-19 in adults: • with positive results of direct SARS-CoV-2 viral testing, and • who are at high risk for progression to severe COVID-19, including hospitalization or death. Refer to CDC website for additional details, and for • whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate. Approved Available Alternatives Although Veklury is an approved alternative treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, FDA does not consider Veklury to be an adequate alternative to Lagevrio for this authorized use because it may not be feasible or practical for certain patients (e.g., it requires an intravenous infusion daily for three days) LIMITATIONS OF AUTHORIZED USE • Molnupiravir is not authorized for use in patients who are less than 18 years of age • Molnupiravir is not authorized for initiation of treatment in patients hospitalized due to COVID-19. Benefit of treatment with molnupiravir has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19 • Molnupiravir is not authorized for use for longer than 5 consecutive days. • Molnupiravir is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

	Molnupiravir may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which molnupiravir belongs (i.e., anti-infectives). Molnupiravir is not approved for any use, including for use for the treatment of COVID-19 **DOSAGE AND ADMINISTRATION** The dosage in adult patients is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food. Take molnupiravir as soon as possible after a diagnosis of COVID-19 has been made, **and within 5 days of symptom onset**. Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximize viral clearance and minimize transmission of SARS-CoV-2. Molnupiravir is not authorized for use for longer than 5 consecutive days because the safety and efficacy have not been established. Should a patient require hospitalization after starting treatment with molnupiravir, the patient may complete the full 5 day treatment course per the healthcare provider's discretion. **DOSAGE FORMS AND STRENGTHS** • Capsules: 200 mg
Nirmatrelvir and Ritonavir (Paxlovid™)	**AUTHORIZED USE** The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product Paxlovid for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk1 for progression to severe COVID-19, including hospitalization or death. LIMITATIONS OF AUTHORIZED USE • Paxlovid is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19 • Paxlovid is not authorized for use as pre-exposure or post-exposure prophylaxis for prevention of COVID-19. • Paxlovid is not authorized for use for longer than 5 consecutive days. Paxlovid may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which PAXLOVID belongs (i.e., anti-infectives). Paxlovid is **not** approved for any use, including for use for the treatment of COVID-19. **DOSAGE AND ADMINISTRATION** Paxlovid is nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir must be co-administered with ritonavir. Failure to correctly co-administer nirmatrelvir with ritonavir may result in plasma levels of nirmatrelvir that are insufficient to achieve the desired therapeutic effect.

	The dosage for Paxlovid is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) with all three tablets taken together orally twice daily for 5 days. Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID. Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximize viral clearance and minimize transmission of SARS-CoV-2. The 5-day treatment course of Paxlovid should be initiated as soon as possible after a diagnosis of COVID-19 has been made, **and within 5 days of symptom onset**. Should a patient require hospitalization due to severe or critical COVID-19 after starting treatment with Paxlovid, the patient should complete the full 5-day treatment course per the\ healthcare provider's discretion. **DOSAGE FORMS AND STRENGTHS** Paxlovid is nirmatrelvir tablets co-packaged with ritonavir tablets. • Nirmatrelvir is supplied as oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Each tablet contains 150 mg of nirmatrelvir. • Ritonavir is supplied as white film-coated ovaloid tablets debossed with the "a" logo and the code NK. Each tablet contains 100 mg of ritonavir.
Regiocit	**<u>Important Administration Instructions:</u>** • A separate systemic infusion of calcium must be administered during use of Regiocit to prevent or treat hypocalcemia. Blood calcium concentrations (ionized and total) must be monitored throughout CRRT. • Regiocit solution must be used in pre-dilution mode only, with appropriate extracorporeal renal replacement equipment intended for CRRT, using an integrated preblood pump for RCA and in combination with other replacement and/or dialysate solution to provide the recommended dose of CRRT. • Regiocit may only be administered by health care providers/institutions that have been qualified by Baxter to administer the product. <u>Administration Instructions</u> • Renal Replacement Solution: **For Extracorporeal use only. Not for direct intravenous infusion.** • The recommended effluent volume for patients receiving CRRT for acute kidney injury (AKI) is 20 to 25 mL/kg/h. This usually requires a higher prescription of effluent volume. The prescription of Regiocit solution must consider the flow rates of the effluent and other therapeutic fluids, the patient's fluid removal requirements, additional fluid inputs and outputs, and the desired acid-base and electrolyte balance. • The mode of therapy, solute formulations, flow rates and length of therapy should be selected by the physician responsible for managing treatment depending on the clinical condition of the patient as well as the patient's fluid, electrolyte, acid base and glucose balance. • Dialysate and replacement fluid formulations and flow rates are prescribed in accordance with the patient's clinical needs. The use of a calcium-containing dialysate or replacement fluid is not recommended, since the calcium provided by these solutions may counteract the anticoagulant effect of citrate in the circuit. <u>Suggested Dosing</u> • The rate at which Regiocit solution is administered depends on the targeted citrate dose and the prescribed blood flow rate. The pre-filter infusion rate of Regiocit solution is indexed to the blood flow rate to achieve a target blood citrate concentration of 3 mmol/L of blood (See Table 1). Flow rate for anticoagulation of the extracorporeal circuit should be titrated to achieve a post-filter concentration of ionized calcium in the range of 0.25 to 0.35 mmol/L.

<table>
<tr><td></td><td>
Table 1: Regiocit Solution Flow Rates to Achieve Citrate Dose of 3 mmol/L of Blood
<table>
<tr><th>Blood flow rate (mL/min)</th><th>Regiocit solution flow rate (mL/h)</th></tr>
<tr><td>100</td><td>1000</td></tr>
<tr><td>110</td><td>1100</td></tr>
<tr><td>120</td><td>1200</td></tr>
<tr><td>130</td><td>1300</td></tr>
<tr><td>140</td><td>1400</td></tr>
<tr><td>150</td><td>1500</td></tr>
<tr><td>160</td><td>1600</td></tr>
<tr><td>170</td><td>1700</td></tr>
<tr><td>180</td><td>1800</td></tr>
<tr><td>190</td><td>1900</td></tr>
<tr><td>200</td><td>2000</td></tr>
</table>

Prior to initiating therapy, the patient’s systemic ionized calcium concentration should be within the normal physiologic range (1.0 to 1.2 mmol/L) by adjustment of calcium supplementation. A separate infusion of calcium is always required during use of Regiocit, due to loss in the effluent. Calcium solution infusion is commenced at the rate of 4 mmol/h, when commencing therapy (see Table 4 in HCP Fact Sheet for more information).
Adjust or stop calcium infusion according to physician’s prescription when Regiocit is stopped. Citrate also acts as a buffer source (due to conversion to bicarbonate); the infusion rate of Regiocit solution must be considered in relation to the rate at which buffer administration occurs from other sources (e.g., dialysate and/or replacement fluid). Regiocit solution must be used together with a dialysis solution/replacement solution with appropriate bicarbonate concentration.

</td></tr>
<tr><td>Remdesivir (Veklury®)</td><td>
Revoked on April 25, 2022; refer to Veklury’s prescribing information for below information.

<u>Patient Selection and Treatment Initiation</u>

Patients with positive results of direct SARS-CoV-2 viral testing.
The treatment course of Veklury should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made and for non-hospitalized patients, within 7 days of symptom onset.
Pediatric patients (greater than 28 days old) must have an estimated glomerular filtration rate (eGFR) determined and full-term neonates (at least 7 days to less than or equal to 28 days old) must have serum creatinine determined before starting Veklury and be monitored during treatment as clinically appropriate.
Perform hepatic laboratory testing in all patients before starting Veklury and during treatment as clinically appropriate.
Determine prothrombin time in all patients before starting Veklury and monitor during treatment as clinically appropriate

The only authorized dosage form of Veklury for pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg is Veklury for injection (supplied as 100 mg lyophilized powder in vial).

Veklury must be administered by intravenous (IV) infusion.

For pediatric patients weighing 3.5 kg to less than 40 kg, administer a body weight-based dosing regimen of Veklury via intravenous (IV) infusion. The dosage should be calculated using the mg/kg dose according to the patient’s weight.
</td></tr>
</table>

<table>
<tr><td></td><td>For pediatric patients less than 12 years of age and weighing 40 kg and higher, administer a single loading dose of Veklury 200 mg on Day 1 followed by once-daily maintenance doses of Veklury 100 mg from Day 2.

Refer to Table 1 below for recommended dosage form and dosage in pediatric patients according to weight [see Dosage and Administration.

Table 1: Recommended Dosage Form and Dosage in Pediatric Patients
<table>
<tr><th>Body Weight</th><th>Recommended dosage form</th><th>Loading Dose (on Day 1)</th><th>Maintenance dose (from Day 2)</th></tr>
<tr><td>3.5 kg to less than 40 kg</td><td rowspan="2">Veklury (remdesivir) Lyophilized Powder for Injection Only</td><td>5 mg/kg</td><td>2.5 mg/kg</td></tr>
<tr><td>40 kg and higher</td><td>200 mg</td><td>100 mg</td></tr>
</table>
Hospitalized patients:
• The treatment course of Veklury should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made.
• The recommended total treatment duration for hospitalized patients requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) is 10 days.
• The recommended treatment duration for hospitalized patients not requiring invasive mechanical ventilation and/or ECMO is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days for a total treatment duration of up to 10 days.

Non-hospitalized patients:
• The treatment course of VEKLURY should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made and within 7 days of symptom onset.
• The recommended total treatment duration for non-hospitalized patients diagnosed with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, is 3 days.

Veklury for injection must be reconstituted and further diluted prior to intravenous infusion.</td></tr>
<tr><td>Sotrovimab</td><td>AUTHORIZED USE

Sotrovimab is authorized for use under an Emergency Use Authorization (EUA) for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) 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 progression to severe COVID-19, including hospitalization or death [see Clinical Trial Results and Supporting Data for EUA (18)].

LIMITATIONS OF AUTHORIZED USE
• Sotrovimab is not authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency.
o FDA’s determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.
• Sotrovimab is NOT authorized for use in patients:
o who are hospitalized due to COVID-19, OR</td></tr>
</table>

	o who require oxygen therapy due to COVID-19, OR o 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). Benefit of treatment with sotrovimab has not been observed in patients hospitalized due to • COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Sotrovimab has been authorized by FDA for the emergency use described above. Sotrovimab is **not** FDA-approved for this use. High Risk The following medical conditions or other factors may place adults and pediatric patients (12 to 17 years of age weighing at least 40 kg) at higher risk for progression to severe COVID-19: • Older age (for example ≥65 years of age) • Obesity or being overweight (for example, adults with BMI >25 kg/m2, or if 12 to 17 years of age, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://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]) 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 sotrovimab under the EUA is 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: https://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. Prescribing Information **Sotrovimab must be administered after dilution by intravenous (IV) infusion.** The authorized dosage for sotrovimab is one single IV infusion of 500 mg administered as soon as possible after a positive viral test for SARS-CoV-2 and within 10 days of symptom onset [see Dosage and Administration (2.2) and Clinical Trial Results and Supporting Data for EUA (18)]. • Sotrovimab is available as a concentrated solution and must be diluted prior to administration.

	• Administer 500 mg of sotrovimab by IV infusion over 30 minutes. • Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete. <u>Antiviral Resistance</u> There is a potential risk of treatment failure due to the development of viral variants that are resistant to sotrovimab. Prescribing healthcare providers should choose an authorized therapeutic option with activity against circulating SARS-CoV-2 variants in their state. SARS-CoV-2 variant frequency data for states and jurisdictions can be accessed on the CDC website available at: https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fvariant-proportions.html#variant-proportions. Please consult the Sotrovimab Fact Sheet For Healthcare Providers for the latest sotrovimab microbiology/antiviral resistance information.
Tixagevimab and cilgavimab (Evusheld)	**<u>AUTHORIZED USE</u>** The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product Evusheld (tixagevimab co-packaged with cilgavimab) for the pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in 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 an individual infected with SARS-CoV-2 and o 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 o 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). Evusheld has been authorized by FDA for the emergency use described above. Evusheld is **<u>not</u>** FDA-approved for any use, including use for pre-exposure prophylaxis of COVID-19. 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 2 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 <200/mm^3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV) • Active treatment with high-dose corticosteroids (i.e. ≥ 20 mg prednisone or equivalent per day when administered for ≥ 2 weeks), 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)

	DOSAGE AND ADMINISTRATION Initial Dosing The dosage of Evusheld in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) is **300 mg of tixagevimab and 300 mg of cilgavimab** administered as two separate consecutive intramuscular (IM) injections. Dosing for Individuals Who Initially Received 150 mg of Tixagevimab and 150 mg of Cilgavimab • Individuals who have already received the previously authorized initial dose (150 mg of tixagevimab and 150 mg of cilgavimab) **should receive an additional Evusheld dose as soon as possible, with the dose based on the following criteria**: o If the patient received their initial dose ≤ 3 months ago, the patient should receive a dose of 150 mg of tixagevimab and 150 mg of cilgavimab o If the patient received their initial dose > 3 months ago, the patient should receive a dose of 300 mg of tixagevimab and 300 mg of cilgavimab Repeat Dosing The repeat dosage of EVUSHELD in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) is 300 mg of tixagevimab and 300 mg of cilgavimab administered **every 6 months**. Repeat dosing should be timed from the date of the most recent Evusheld dose. The recommendations for dosing are based on the totality of the scientific evidence including clinical pharmacology data, antiviral activity data, and clinical trial data. Evusheld has only been studied for the prophylaxis of COVID-19 at the Evusheld (150 mg of tixagevimab and 150 mg of cilgavimab) dose. There are no data available in a prophylaxis setting for the Evusheld (300 mg of tixagevimab and 300 mg of cilgavimab) dose. The clinical safety of the Evusheld (300 mg of tixagevimab and 300 mg of cilgavimab) dose is supported by safety data from a treatment study in subjects with mild to moderate COVID-19. There are limited safety and no efficacy data available with repeat dosing. **DOSAGE FORMS AND STRENGTHS** Injection: • tixagevimab 150 mg/1.5 mL (100 mg/mL) in a single-dose vial • cilgavimab 150 mg/1.5 mL (100 mg/mL) in a single-dose vial
Tocilizumab (Actemra IV)	**AUTHORIZED USE** The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of ACTEMRA (tocilizumab) for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. However, ACTEMRA is not FDA-approved for this use. ACTEMRA is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of ACTEMRA under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner. Recommended Dosage for COVID-19 The recommended dosage for emergency use of ACTEMRA authorized under this EUA given as a single 60-minute intravenous infusion is:

	<table><tr><th colspan="2">Recommended Intravenous Dosage for COVID-19</th></tr><tr><td>Patients less than 30 kg weight</td><td>12 mg/kg</td></tr><tr><td>Patients at or above 30 kg weight</td><td>8 mg/kg</td></tr></table> If clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of ACTEMRA may be administered at least 8 hours after the initial infusion. Maximum Dosage in COVID-19 patients is 800 mg per infusion. ACTEMRA subcutaneous administration is NOT authorized for the treatment of COVID-19 patients.

FDA EUA Letter

Bamlanivimab and Etesevimab

Date	EUA Letter
1/24/2022	On January 24, 2022, again having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the December 22, 2021 letter in its entirety, to further limit the use of bamlanivimab and etesevimab administered together for treatment of COVID-19 or as post-exposure prophylaxis of COVID-19 to exclude geographic regions where, based on available information including variant susceptibility to these drugs and regional variant frequency, infection or exposure is likely due to a variant that is non-susceptible to bamlanivimab and etesevimab. Corresponding revisions have also been made to the authorized Fact Sheets. **Scope of Authorization** • Distribution of the authorized bamlanivimab and etesevimab will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Lilly will supply bamlanivimab and etesevimab to authorized distributors, who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed *Treatment of COVID-19* • The bamlanivimab and etesevimab covered by this authorization will be administered together only by healthcare providers to treat mild to moderate COVID-19 in adults and pediatric patients, including neonates, with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death; • Bamlanivimab and etesevimab may only be administered together; • Bamlanivimab and etesevimab are authorized for use only in states, territories, and U.S. jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab administered together is less than or equal to 5%, as determined by FDA. A list of states, territories and U.S. jurisdictions in which bamlanivimab and etesevimab are and are not8 currently authorized is available on FDA's website at: https://www.fda.gov/media/151719/download; • Bamlanivimab and etesevimab are **not** authorized for use in patients 2 years of age and older who are hospitalized due to COVID-19 o Treatment with bamlanivimab and etesevimab has not been studied in patients hospitalized due to COVID-19. However, the reasons for hospital admission may be different and the threshold for hospital admission may be lower for neonates, young infants and toddlers with COVID-19 compared to older children and adults. This authorization covers young children (i.e., birth to 2 years of age) who are

Date	EUA Letter
	hospitalized with mild to moderate COVID-19 at the time of treatment to receive bamlanivimab and etesevimab. • Bamlanivimab and etesevimab are **not** authorized for use in the following patient populations, regardless of age: o Require oxygen therapy due to COVID-19, or o Require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity • Bamlanivimab and etesevimab are not authorized for treatment of mild to moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant, based on available information including variant susceptibility to these drugs and regional variant frequency. • Bamlanivimab and etesevimab may only be administered together in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary; • The use of bamlanivimab and etesevimab covered by this authorization must be in accordance with the authorized Fact Sheets *Post-Exposure Prophylaxis of COVID-19* • Bamlanivimab and etesevimab administered together may only be used in adult and pediatric individuals, including neonates, for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are: o not fully vaccinated **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications) **and** ▪ have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC) **or** ▪ who are at high risk of exposure to an individual infected with SARSCoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons). • Bamlanivimab and etesevimab may only be administered together • Bamlanivimab and etesevimab are authorized for use **only** in states, territories, and U.S. jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab administered together is less than or equal to 5%, as determined by FDA. o A list of states, territories and U.S. jurisdictions in which bamlanivimab and etesevimab are and are not14 currently authorized is available on FDA's website at: https://www.fda.gov/media/151719/download; • Bamlanivimab and etesevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary. • The use of bamlanivimab and etesevimab covered by this authorization must be in accordance with the authorized Fact Sheets. • Post-exposure prophylaxis with bamlanivimab and etesevimab administered together is **not** intended to be a substitute for vaccination against COVID-19. • Bamlanivimab and etesevimab administered together is **not** authorized for pre-exposure prophylaxis for prevention of COVID-19
12/3/2021	On December 3, 2021, again having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the September 16, 2021 letter in its entirety, to also authorize bamlanivimab and etesevimab administered together for emergency use as treatment for COVID-19 and as post-exposure

Date	EUA Letter
	prophylaxis of COVID-19 in certain younger pediatric individuals, including neonates, not covered under prior authorizations. **Scope of Authorization** • Distribution of the authorized bamlanivimab and etesevimab will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Lilly will supply bamlanivimab and etesevimab to authorized distributors, who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed *Treatment of COVID-19* • The bamlanivimab and etesevimab covered by this authorization will be administered together only by healthcare providers to treat mild to moderate COVID-19 in adults and pediatric patients, including neonates, with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death; • Bamlanivimab and etesevimab may only be administered together; • Bamlanivimab and etesevimab are authorized for use only in states, territories, and U.S. jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab administered together is less than or equal to 5%, as determined by FDA. A list of states, territories and U.S. jurisdictions in which bamlanivimab and etesevimab are and are not8 currently authorized is available on FDA's website at: https://www.fda.gov/media/151719/download; • Bamlanivimab and etesevimab are **not** authorized for use in patients 2 years of age and older who are hospitalized due to COVID-19 o Treatment with bamlanivimab and etesevimab has not been studied in patients hospitalized due to COVID-19. However, the reasons for hospital admission may be different and the threshold for hospital admission may be lower for neonates, young infants and toddlers with COVID-19 compared to older children and adults. This authorization covers young children (i.e., birth to 2 years of age) who are hospitalized with mild to moderate COVID-19 at the time of treatment to receive bamlanivimab and etesevimab. • Bamlanivimab and etesevimab are **not** authorized for use in the following patient populations, regardless of age: o Require oxygen therapy due to COVID-19, or o Require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity • Bamlanivimab and etesevimab may only be administered together in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary; • The use of bamlanivimab and etesevimab covered by this authorization must be in accordance with the authorized Fact Sheets *Post-Exposure Prophylaxis of COVID-19* • Bamlanivimab and etesevimab administered together may only be used in adult and pediatric individuals, including neonates, for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are: o not fully vaccinated **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications) **and**

Date	EUA Letter
	▪ have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC) **or** ▪ who are at high risk of exposure to an individual infected with SARSCoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons). • Bamlanivimab and etesevimab may only be administered together • Bamlanivimab and etesevimab are authorized for use **only** in states, territories, and U.S. jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab administered together is less than or equal to 5%, as determined by FDA. o A list of states, territories and U.S. jurisdictions in which bamlanivimab and etesevimab are and are not14 currently authorized is available on FDA's website at: https://www.fda.gov/media/151719/download; • Bamlanivimab and etesevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary. • The use of bamlanivimab and etesevimab covered by this authorization must be in accordance with the authorized Fact Sheets. • Post-exposure prophylaxis with bamlanivimab and etesevimab administered together is **not** intended to be a substitute for vaccination against COVID-19. • Bamlanivimab and etesevimab administered together is **not** authorized for pre-exposure prophylaxis for prevention of COVID-19
9/16/2021	On September 16, 2021, again having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the August 27, 2021 letter in its entirety, to also authorize bamlanivimab and etesevimab administered together for emergency use as post-exposure prophylaxis in certain adults and pediatric individuals. **Scope of Authorization** • Distribution of the authorized bamlanivimab and etesevimab will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Lilly will supply bamlanivimab and etesevimab to authorized distributors6, who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed *Treatment of COVID-19* • The bamlanivimab and etesevimab covered by this authorization will be administered together only by healthcare providers to treat mild to moderate COVID-19 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 progression to severe COVID-19, including hospitalization or death; • Bamlanivimab and etesevimab may only be administered together; • Bamlanivimab and etesevimab are authorized for use only in states, territories, and U.S. jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab administered together is less than or equal to 5%, as determined by FDA. A list of states, territories and U.S. jurisdictions in which bamlanivimab and etesevimab are and are not8 currently authorized is available on FDA's website at: https://www.fda.gov/media/151719/download; • Bamlanivimab and etesevimab are not authorized for use in the following patient populations: o Adults or pediatric patients who are hospitalized due to COVID-19, or o Adults or pediatric patients who require oxygen therapy due to COVID-19, or

Date	EUA Letter
	o Adults or pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity Bamlanivimab and etesevimab may only be administered together in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary; • The use of bamlanivimab and etesevimab covered by this authorization must be in accordance with the authorized Fact Sheets *Post-Exposure Prophylaxis of COVID-19* • Bamlanivimab and etesevimab administered together may only be used in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are: o not fully vaccinated **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications) **and** ▪ have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC) **or** ▪ who are at high risk of exposure to an individual infected with SARSCoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons). • Bamlanivimab and etesevimab may only be administered together • Bamlanivimab and etesevimab are authorized for use **only** in states, territories, and U.S. jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab administered together is less than or equal to 5%, as determined by FDA. A list of states, territories and U.S. jurisdictions in which bamlanivimab and etesevimab are and are not14 currently authorized is available on FDA's website at: https://www.fda.gov/media/151719/download; • Bamlanivimab and etesevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary. • The use of bamlanivimab and etesevimab covered by this authorization must be in accordance with the authorized Fact Sheets. • Post-exposure prophylaxis with bamlanivimab and etesevimab administered together is not intended to be a substitute for vaccination against COVID-19. • Bamlanivimab and etesevimab administered together is **not** authorized for pre-exposure prophylaxis for prevention of COVID-19
8/27/2021	On August 27, 2021 FDA and ASPR announced the authorization of the use the use of bamlanivimab and etesevimab, administered together, only in states, territories, and U.S. jurisdictions in which recent data shows the combined frequency of variants resistant to bamlanivimab and etesevimab administered together is less than or equal to 5%. Bamlanivimab and etesevimab, administered together, will not be authorized for use in states, territories, and U.S. jurisdictions in which recent data shows the combined frequency of variants resistant to bamlanivimab and etesevimab administered together exceeds 5%. FDA has posted a list of states, territories, and U.S. jurisdictions in which bamlanivimab and etesevimab administered together are currently authorized, and a list of states, territories, and U.S. jurisdictions in which bamlanivimab and etesevimab, administered together, are not currently authorized and will periodically update both lists as new data and information becomes available. FDA will make this determination considering current variant frequency

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	data, trends in variant frequency over time, and the precision of the estimates and information regarding emerging variants of concern. Both REGEN-COV and Sotrovimab are available under FDA's Emergency Use Authorization for the treatment of eligible patients. (ASPR/FDA, 2021b)
6/25/2021	On June 25, 2021 the Assistant Secretary for Preparedness and Response (ASPR) and the Food and Drug Administration (FDA) issued a pause on all distribution of bamlanivimab and etesevimab together and etesevimab alone (to pair with existing supply of bamlanivimab at a facility for use under EUA (094) on a national basis until further notice. In addition, FDA recommends that health care providers nationwide use alternative authorized monoclonal antibody therapies, as described below, and not use bamlanivimab and etesevimab administered together at this time. The Centers for Disease Control and Prevention (CDC) has identified that the combined frequencies of the SARS-CoV-2 P.1/Gamma variant (first identified in Brazil) and the B.1.351/Beta variant (first identified in South Africa) throughout the United States now exceed 11% and are trending upward (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html). Results from in vitro assays that are used to assess the susceptibility of viral variants to particular monoclonal antibodies suggest that bamlanivimab and etesevimab administered together are not active against either the P.1 or B.1.351 variants. These assays use "pseudotyped virus-like particles" that help determine likely susceptibility of the live SARS-CoV-2 variant viruses. (ASPR/FDA, 2021a)
2/9/2021	The FDA issued an EUA on February 9, 2021 for emergency use of bamlanivimab and etesevimab administered together for the treatment of mild to moderate coronavirus disease 2019 (COVID-19). (U.S. FDA EUA, 2020f) Bamlanivimab and etesevimab are neutralizing IgG1 monoclonal antibodies that bind to distinct but overlapping epitopes within the receptor binding domain of the spike protein of SARS-CoV2. They are both investigational drugs and are not currently approved for any indication. Scope of Authorization: • Distribution of the authorized bamlanivimab and etesevimab will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Lilly will supply bamlanivimab and etesevimab to authorized distributors, who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed; • The bamlanivimab and etesevimab covered by this authorization will be administered together only by healthcare providers to treat mild to moderate COVID-19 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 • Etesevimab may only be administered together with bamlanivimab • Bamlanivimab and etesevimab are not authorized for use in the following patient populations o Adults or pediatric patients who are hospitalized due to COVID-19 o Adults or pediatric patients who require oxygen therapy due to COVID19 o Adults or pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity. • Bamlanivimab and etesevimab may only be administered together in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

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	• The use of bamlanivimab and etesevimab covered by this authorization must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets.

Product Description
Bamlanivimab and etesevimab are neutralizing IgG1 monoclonal antibodies that bind to distinct but overlapping epitopes within the receptor binding domain of the spike protein of SARS-CoV2.

Bamlanivimab injection, 700 mg/20 mL, and etesevimab, 700 mg/20 mL, are sterile, preservative-free clear to opalescent and colorless to slightly yellow to slightly brown solutions to be diluted prior to infusion.

Baricitinib (Olumiant)

Date	EUA Letter
5/10/2022	On May 10, 2022, FDA approved a supplement to NDA 207924 for baricitinib for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. Having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA is reissuing the December 20, 2021 letter in its entirety with revisions to the scope of authorization to continue authorizing baricitinib for the treatment of COVID-19 in hospitalized pediatric patients 2 to less than 18 years of age requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO and removing the adult population covered under the approved indication. **Scope of Authorization** • The baricitinib covered by this authorization will be used only by healthcare providers to treat COVID-19 in hospitalized pediatric patients 2 to less than 18 years of age requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO; and • The use of baricitinib covered by this authorization must be in accordance with the authorized Fact Sheets
7/28/2021	The FDA re-issued the EUA for baricitinib on July 28, 2021 in its entirety with revision incorporated. The revision included removal of the concurrent administration with remdesivir. Baricitinib now has an EUA as monotherapy to treat COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. (U.S. FDA EUA, 2020d) Scope of Authorization: • The baricitinib covered by this authorization will be used only by healthcare providers to treat COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO; and • The use of baricitinib covered by this authorization must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets While this Letter of Authorization authorizes the use of baricitinib alone for the uses detailed in the Scope of Authorization, the Agency notes that the COV-BARRIER trial supporting this authorization did not raise questions about the safety or efficacy of baricitinib used in combination with remdesivir for the treatment of patients hospitalized due to COVID-19 requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. As such, the use of baricitinib in combination with remdesivir is not contraindicated under the terms and conditions of this authorization.
11/19/2020	The FDA issued a EUA on November 19, 2020 for emergency use of baricitinib (Olumiant), in combination with remdesivir (Veklury), for the treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in certain hospitalized patients requiring

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	supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). (U.S. FDA EUA, 2020d) Baricitinib (Olumiant) is approved by FDA for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor antagonist therapies. Baricitinib has not been approved by FDA for the treatment of COVID-19. Scope of Authorization: • The baricitinib covered by this authorization will be used only by healthcare providers, in combination with remdesivir, to treat suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO; and • The use of baricitinib covered by this authorization must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets.

Product Description
Baricitinib is a Janus kinase (JAK) inhibitor. Baricitinib is available as debossed, film-coated, immediate-release tablets. Each tablet contains a recessed area on each face of the tablet surface. Baricitinib tablets are to be taken orally or can be crushed, dispersed in water, and given via a gastrostomy tube. The authorized baricitinib includes commercially available Olumiant (baricitinib) supplied in 30 count bottles as follows:

- OLUMIANT (baricitinib) 1 mg (NDC 0002-4732-30)
- OLUMIANT (baricitinib) 2 mg (NDC 0002-4182-30)

Bebtelovimab

Date	EUA Letter
2/11/2022	On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19). On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section. Bebtelovimab is a neutralizing IgG1 monoclonal antibody that binds to an epitope within the receptor binding domain of the spike protein of SARS-CoV-2. Bebtelovimab is not FDA-approved for any uses, including use as treatment for COVID-19. Based on the review of the data from the BLAZE-4 clinical trial (NCT04634409), a Phase 1/2 randomized, single-dose clinical trial studying bebtelovimab for the treatment of non-hospitalized patients with mild-to-moderate COVID-19, as well as available pharmacokinetic data and nonclinical viral neutralization data for Omicron and other variants of concern, it is reasonable to believe that bebtelovimab may be effective for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high-risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate, as described in the Scope of Authorization. **Scope of Authorization**

	• Distribution of the authorized bebtelovimab will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Lilly will supply bebtelovimab to authorized distributor(s)5 , who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed • Bebtelovimab may only be used for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg): o With positive results of direct SARS-CoV-2 viral testing, and o Who are at high-risk6 for progression to severe COVID, including hospitalization or death, and o For whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. • Bebtelovimab is **not** authorized for use in the following patient populations: o Adults or pediatric patients who are hospitalized due to COVID-19, or o Adults or pediatric patients who require oxygen therapy and/or respiratory support due to COVID-19, or o Adults or pediatric patients who require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 in those patients on chronic oxygen therapy and/or oxygen support due to underlying non-COVID-19- related comorbidity; • Bebtelovimab is **not** authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant, based on available information including variant susceptibility to these drugs and regional variant frequency. • Bebtelovimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary; • The use of bebtelovimab covered by this authorization must be in accordance with the authorized Fact Sheets.

Product Description
Bebtelovimab is a neutralizing IgG1 monoclonal antibody that binds to an epitope within the receptor binding domain of the spike protein of SARS-CoV-2. Bebtelovimab is not FDA approved for any uses, including use as treatment for COVID-19.

Casirivimab and Imdevimab (REGEN-COV)

Date	EUA Letter
1/24/2022	On January 24, 2022, again having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the November 17, 2021 letter in its entirety, to further limit the use of REGEN-COV for treatment of COVID-19 or as post-exposure prophylaxis of COVID-19 to exclude geographic regions where, based on available information including variant susceptibility to this drug and regional variant frequency, infection or exposure is likely due to a variant that is non-susceptible to REGEN-COV. Corresponding revisions have also been made to the authorized Fact Sheets. **Scope of Authorization:**

	Treatment of COVID-19 • REGEN-COV will be used only by healthcare providers to treat mild to moderate COVID-19 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, including hospitalization or death; • The monoclonal antibodies that comprise REGEN-COV, casirivimab and imdevimab, may only be administered together • REGEN-COV is <u>not</u> authorized for use in the following patient populations10: o Adults or pediatric patients who are hospitalized due to COVID-19, or o Adults or pediatric patients who require oxygen therapy due to COVID19, or o Adults or pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity. • REGEN-COV is not authorized for treatment of mild to moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant, based on available information including variant susceptibility to this drug and regional variant frequency • REGEN-COV may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary. • REGEN-COV is authorized for intravenous infusion. Subcutaneous injection is authorized as an alternative route of administration when intravenous infusion is not feasible and would lead to delay in treatment. • The use of REGEN-COV covered by this authorization must be in accordance with the authorized Fact Sheets. ***Post-Exposure Prophylaxis*** • REGEN-COV may only be used in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are: o not fully vaccinated or who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications) **AND** ▪ have been exposed* to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)**; **OR** ▪ who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) • REGEN-COV is not authorized for post-exposure prophylaxis of COVID-19 in geographic regions where exposure is likely to have been to a non-susceptible SARS-CoV-2 variant, based on available information including variant susceptibility to these drugs and regional variant frequency. • The monoclonal antibodies that comprise REGEN-COV, casirivimab and imdevimab, may only be administered together; • REGEN-COV may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary. • REGEN-COV is authorized for <u>either intravenous infusion or subcutaneous injection</u> when administered for post-exposure prophylaxis under this authorization.

	• The use of REGEN-COV covered by this authorization must be in accordance with the authorized Fact Sheets. • Post-exposure prophylaxis with REGEN-COV (casirivimab with imdevimab) is not intended to be a substitute for vaccination against COVID-19. • **REGEN-COV is <u>NOT</u> authorized for pre-exposure prophylaxis for prevention of COVID-19**. *<u>Note</u>: *Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as the Johnson & Johnson/ Janssen vaccine).* **<u>Note</u>: *Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example).*
7/30/2021	On July 30, 2021, again having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the June 3, 2021 letter in its entirety, to also authorize REGEN-COV for emergency use as post-exposure prophylaxis in certain adults and pediatric individuals. Based on the review of the topline analysis of phase 3 data from COV-2069 (NCT04452318), a phase 3 randomized, double-blind, placebo-controlled trial in household contacts with close exposure to a household member known to be infected with SARS-CoV-2 (index case), but who were themselves asymptomatic; and the analysis of phase 1 data from COV-2093 (NCT 04519437), an ongoing, phase 1, randomized, double-blind, placebo-controlled clinical trial assessing the safety and pharmacokinetics of repeat subcutaneous doses of REGEN-COV in subjects who are SARS-CoV-2 negative at baseline, it is reasonable to believe that REGEN-COV may be effective for use as post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization, and that, when used under such conditions, the known and potential benefits of REGEN-COV outweigh the known and potential risks of such product. Distribution of the authorized REGEN-COV will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Regeneron will supply REGEN-COV to authorized distributor(s), who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed. **Scope of Authorization:** ***Treatment of COVID-19*** • REGEN-COV will be used only by healthcare providers to treat mild to moderate COVID-19 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, including hospitalization or death; • The monoclonal antibodies that comprise REGEN-COV, casirivimab and imdevimab, may only be administered together • REGEN-COV is <u>not</u> authorized for use in the following patient populations10: o Adults or pediatric patients who are hospitalized due to COVID-19, or o Adults or pediatric patients who require oxygen therapy due to COVID19, or o Adults or pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity.

	• REGEN-COV may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary. • REGEN-COV is authorized for intravenous infusion. Subcutaneous injection is authorized as an alternative route of administration when intravenous infusion is not feasible and would lead to delay in treatment. • The use of REGEN-COV covered by this authorization must be in accordance with the authorized Fact Sheets. ***Post-Exposure Prophylaxis*** • REGEN-COV may only be used in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are: o not fully vaccinated or who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications) **AND** ▪ have been exposed* to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)**; **OR** ▪ who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) • The monoclonal antibodies that comprise REGEN-COV, casirivimab and imdevimab, may only be administered together; • REGEN-COV may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary. • REGEN-COV is authorized for <u>either intravenous infusion or subcutaneous injection</u> when administered for post-exposure prophylaxis under this authorization. • The use of REGEN-COV covered by this authorization must be in accordance with the authorized Fact Sheets. • Post-exposure prophylaxis with REGEN-COV (casirivimab with imdevimab) is not intended to be a substitute for vaccination against COVID-19. • **REGEN-COV is <u>NOT</u> authorized for pre-exposure prophylaxis for prevention of COVID-19**. **Note*: Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as the Johnson & Johnson/ Janssen vaccine).* ***Note*: Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example).*
6/3/2021	On June 3, 2021, again having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the February 25, 2021 letter in its entirety, authorizing revisions to the authorized use6 for REGEN-COV, a change in dosing of REGEN-COV from 2400 mg (1200 mg casirivimab and 1200 mg imdevimab) to 1200 mg (600 mg casirivimab and 600 mg imdevimab), and the addition of a

	new presentation consisting of a single vial containing casirivimab and imdevimab co-formulated in a 1:1 ratio for either intravenous infusion or subcutaneous injection. New conditions have been incorporated on the provision of samples of the authorized REGEN-COV to the U.S. Department of Health and Human Services, upon request, and the submission of certain genomic sequencing and virology information to the FDA by a specified date. Revisions to existing conditions on advertising and promotion and manufacturing practices and other editorial changes have also been incorporated. Based on review of the analysis of phase 3 data from COV-20677 (NCT04425629), a phase 1/2/3 randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of a single intravenous infusion of 600 mg casirivimab and 600 mg imdevimab in outpatients (non-hospitalized) with SARS-CoV-2 infection, it is reasonable to believe that REGEN-COV may be effective for the treatment of mild to moderate COVID-19 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 progression to severe COVID-19, including hospitalization or death, and that, when used under the conditions described in this authorization, the known and potential benefits of REGEN-COV outweigh the known and potential risks of such product.
11/21/2020	The FDA issued an EUA on November 19, 2020 for emergency use of casirivimab and imdevimab, administered together, for the treatment of mild to moderate coronavirus disease 2019 (COVID-19). (U.S. FDA EUA, 2020e) Casirivimab and imdevimab are recombinant human IgG1 monoclonal antibodies that target the receptor binding domain of the spike protein of SARS-CoV-2. They are investigational drugs and are not approved for any indication. Scope of Authorization: • Distribution of the authorized casirivimab and imdevimab will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Regeneron will supply casirivimab and imdevimab to authorized distributor(s), who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities, as needed; • The casirivimab and imdevimab covered by this authorization will be used only by healthcare providers to treat mild to moderate COVID-19 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; • Casirivimab and imdevimab may only be administered together; • Casirivimab and imdevimab is not authorized for use in the following patient populations: o Adults or pediatric patients who are hospitalized due to COVID-19, or o Adults or pediatric patients who require oxygen therapy due to COVID19, or o Adults or pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity. • Casirivimab and imdevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary. • The use of casirivimab and imdevimab covered by this authorization must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets

Product description

REGEN-COV is available in dose pack bags that will include a sufficient number of vials of casirivimab and imdevimab to prepare one treatment dose. Casirivimab and imdevimab are each supplied in individual single use

vials. Individual vials and carton container labeling for casirivimab and imdevimab included in dose pack bags are clearly marked “For Use under Emergency Use Authorization.” Casirivimab and imdevimab are recombinant neutralizing human IgG1 monoclonal antibodies that target the receptor binding domain of the spike protein of SARS-CoV-2.

Molnupiravir

Date	EUA Letter
12/23/2021	On December 23, 2021, the FDA issued an emergency use authorization for molnupiravir for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in certain adults who are at high-risk for progression to severe COVID-19, including hospitalization or death. Molnupiravir is a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis. Molnupiravir is not FDA-approved for any uses, including use as treatment for COVID-19. Based on the review of the data from the MOVe-OUT clinical trial (NCT04575597), a Phase III randomized, double-blind, placebo-controlled clinical trial studying molnupiravir for the treatment of non-hospitalized patients with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, it is reasonable to believe that molnupiravir may be effective for the treatment of mild-to-moderate COVID-19 in adults who are at high-risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate, as described in the Scope of Authorization, and when used under the conditions described in this authorization, the known and potential benefits of molnupiravir outweigh the known and potential risks of such product. Scope of Authorization • Distribution of the authorized molnupiravir will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Merck will supply molnupiravir to authorized distributor(s), who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed • Molnupiravir may only be used for the treatment of mild-to-moderate COVID-19 in adults: o With positive results of direct SARS-CoV-2 viral testing, and o Who are at high-risk5 for progression to severe COVID, including hospitalization or death, and o For whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate. <u>Limitations on Authorized Use</u> • Molnupiravir is not authorized for use in patients who are less than 18 years of age. • Molnupiravir is not authorized for initiation of treatment in patients requiring hospitalization due to COVID-19.6 Benefit of treatment with molnupiravir has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19. • Molnupiravir is not authorized for use for longer than 5 consecutive days. • Molnupiravir is not authorized for use as pre-exposure or as post-exposure prophylaxis for prevention of COVID-19. • Molnupiravir may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state7 law to prescribe drugs in the therapeutic class to which molnupiravir belongs (i.e., anti-infectives).

	• The use of molnupiravir covered by this authorization must be in accordance with the authorized Fact Sheets.

Product description
The authorized molnupiravir is supplied as a bottle (NDC-0006-5055-06, NDC-0006-5055-07) containing a sufficient quantity of molnupiravir 200 mg capsules to complete a full treatment course (i.e., 40 capsules).

Nirmatrelvir and ritonavir (Paxlovid)

Date	EUA Letter
7/6/2022	On July 6, 2022, reissued the Letter of Authorization (LOA) its entirety and to authorize state-licensed pharmacists to prescribe Paxlovid subject to certain conditions detailed in Section II (Scope of Authorization) of this LOA. New addition to Scope of Authorization Paxlovid may also be prescribed for an individual patient by a state-licensed pharmacist under the following conditions: • Sufficient information is available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient, to assess renal and hepatic function; and • Sufficient information is available, such as through access to health records, patient reporting of medical history, or consultation with a health care provider in an established provider-patient relationship with the individual patient, to obtain a comprehensive list of medications (prescribed and non-prescribed) that the patient is taking to assess for potential drug interaction
12/22/2022	On December 22, 2021, the FDA issued an emergency use authorization for Paxlovid (nirmatrelvir co-packaged with ritonavir) for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in certain adults and pediatric patients. Paxlovid is comprised of nirmatrelvir, a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor, co-packaged with ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor. Ritonavir, which has no activity against SARS-CoV-2 on its own, is included to inhibit the CYP3A-mediated metabolism of nirmatrelvir and consequently increase nirmatrelvir plasma concentrations to levels anticipated to inhibit SARS-CoV-2 replication. Paxlovid is not approved for any use, including for use for the treatment of COVID-19. Based on the totality of scientific evidence available to FDA, including data from the clinical trial EPIC-HR (NCT04960202), a Phase 2/3 randomized, double blind, placebo-controlled clinical trial, it is reasonable to believe that Paxlovid may be effective for the treatment of mild-to-moderate COVID-19 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 progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization, and when used under the conditions described in this authorization, the known and potential benefits of Paxlovid outweigh the known and potential risks of such product. **Scope of Authorization** • Distribution of the authorized Paxlovid will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Pfizer will supply PAXLOVID to authorized distributor(s), who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed

	• Paxlovid may only be used by healthcare providers to treat mild-to-moderateCOVID-19 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 progression to severe COVID-19, including hospitalization or death <u>Limitations on Authorized Use</u> • Paxlovid is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19 • Paxlovid is not authorized for use as pre-exposure or as post-exposure prophylaxis for prevention of COVID-19 • Paxlovid is not authorized for use for longer than 5 consecutive days • Paxlovid may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which Paxlovid belongs (i.e., anti-infectives) • The use of Paxlovid covered by this authorization must be in accordance with the authorized Fact Sheets

Product description
Paxlovid consists of two 150 mg tablets of nirmatrelvir that are co-packaged with one 100 mg tablet ritonavir.

Regiocit

Date	EUA Letter
8/13/2020	The FDA issued a EUA on August 13, 2020 to permit the emergency use of the unapproved product, Regiocit: a replacement solution that contains citrate for Regional Citrate Anticoagulation (RCA) of the extracorporeal circuit. Regiocit has been authorized for emergency use as a replacement solution in adult patients treated with Continuous Renal Replacement Therapy (CRRT), and for whom RCA is appropriate, during the COVID-19 pandemic. Regiocit is intended for use in a critical care setting. Regiocit is intended to be used in continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodiafiltration (CVVHDF) modalities. Use of Regiocit is limited to healthcare providers and/or institutions that Baxter has qualified to administer Regiocit for these emergency uses. (U.S. FDA EUA, 2020c) Regiocit has been authorized by FDA for emergency use. Regiocit is not FDA-approved. Scope of Authorization: • Regiocit will be used as a replacement solution only in adult patients being treated with CRRT and for whom RCA is appropriate. • Regiocit will be administered only by a licensed healthcare provider in a critical care setting. • Regiocit will be available for use only in facilities that Baxter Healthcare Corporation has qualified for receiving Regiocit.

Product Description
Regiocit (sodium chloride and sodium citrate) solution is for use in adults as replacement solution for regional citrate anticoagulation (RCA) of the extracorporeal circuit in patients treated with continuous renal replacement therapy (CRRT), particularly when systemic anticoagulation with heparin is contraindicated, e.g., in patients with increased bleeding risks.

Regiocit, contains physiological concentrations of sodium (140 mmol/l), chloride (86 mmol/l), and a low concentration of citrate (18 mmol/L). (Regiocit PI, 2020)

Regiocit should be administered only under the supervision of a physician experienced in the use of CRRT.

Remdesivir

Date	EUA Letter
4/25/2022	On April 25, 2022, the Agency approved a supplemental New Drug Application (NDA) to NDA 214787, which expanded the approved indication to the following: *Veklury is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleotide analog RNA polymerase inhibitor indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) with positive results of direct SARS-CoV-2 viral testing, who are:* • Hospitalized, or • Not Hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death. Based on this approval, FDA has concluded that NDA 214787 for Veklury is an adequate, approved, and available alternative to Veklury available for emergency use, for the treatment of COVID-19 for purposes of section 564(c)(3) of the Act. Accordingly, FDA revokes EUA 046 for emergency use of Veklury, pursuant to section 564(g)(2) of the Act. As of the date of this letter, the Veklury that was authorized by FDA for emergency use under EUA 046 is no longer authorized by FDA.
1/21/22022	On January 21, 2022, FDA approved a supplemental application to NDA 214787 for Veklury expanding the approved uses to include the treatment of COVID-19 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, who are not hospitalized and have mild-to-moderate COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA is reissuing the October 22, 2020, letter in its entirety with revisions to the scope of authorization now authorizing Veklury for the treatment of COVID-19 in pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg, with positive results of direct SARS-CoV-2 viral testing, who are hospitalized, or are not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death. Based on review and extrapolation of the data from the Gilead-sponsored trial (NCT04501952) evaluating Veklury for the treatment of non-hospitalized patients with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19 disease, it is reasonable to believe that Veklury may be effective for the treatment of pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg, with positive results of direct SARS-CoV-2 viral testing, who are not hospitalized, have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death, and that, when used under such conditions, the known and potential benefits of Veklury outweigh the known and potential risks of such product. **Scope of Authorization:** • Veklury will be used only for the treatment of COVID-19 in pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg, with positive results of direct SARS-CoV-2 viral testing, and who: o Are hospitalized, or o Are not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

Date	EUA Letter
	• The use of Veklury covered by this authorization must be in accordance with the authorized Facts Sheets.
10/22/2020	On October 22, 2020, FDA approved Veklury (remdesivir) for use in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization. Veklury should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care. This approval does not include the entire population that had been authorized to use Veklury under an Emergency Use Authorization (EUA) originally issued on May 1, 2020. In order to ensure continued access to the pediatric population previously covered under the EUA, the EUA for Veklury continues to authorize Veklury for emergency use by licensed healthcare providers for the treatment of suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg. (U.S. FDA EUA, 2020b) **Scope of Authorization:** • The Veklury covered by this authorization will be used only to treat suspected or laboratory-confirmed COVID-19 in hospitalized* pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg administered via intravenous (IV) infusion by a healthcare provider; • The use of Veklury covered by this authorization should be in accordance with the dosing regimens as detailed in the authorized Facts Sheets. *Note: Individuals determined as being appropriate for acute inpatient hospitalization and who are admitted or transferred to an alternate care site (ACS) that is capable of providing acute care that is comparable to general inpatient hospital care are within the terms and conditions of the Letter of Authorization. An ACS is intended to provide additional hospital surge capacity and capability for communities overwhelmed by patients with COVID-19.
8/28/2020	The FDA reissued the May 1, 2020 letter in its entirety with revisions incorporated to expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease. (U.S. FDA EUA, 2020b) **Scope of Authorization:** • Distribution of the authorized Veklury will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Gilead will supply Veklury to authorized distributors[7], or directly to a U.S. government agency, who will distribute to hospitals and other healthcare facilities as directed by the U.S. Government, in collaboration with state and local government authorities, as needed • The Veklury covered by this authorization will be used only to treat adults and children with suspected or laboratory confirmed COVID-19 administered in an in-patient hospital setting via intravenous (IV) infusion by a healthcare provider • The use of Veklury covered by this authorization should be in accordance with the dosing regimens as detailed in the authorized Facts Sheets.
5/1/2020	FDA issued a EUA to allow remdesivir to be distributed and used by licensed health care providers to treat adults and children hospitalized with severe COVID-19.

Product Description

Remdesivir is a direct acting antiviral drug that inhibits viral RNA synthesis. It is an investigational drug and is not currently approved for any indication. Remdesivir has activity in cell culture and animal models against SARS-CoV, MERS-CoV, and SARS-CoV-2. Based on review of the topline data from the randomized, double-blinded, placebo-controlled trial conducted by NIAID (NCT04280705) and from the Gilead-sponsored open-label trial that

evaluated different durations of remdesivir (NCT04292899), it is reasonable to believe that the known and potential benefits of RDV outweigh the known and potential risks of the drug for the treatment of patients hospitalized with severe COVID-19. (U.S. FDA EUA, 2020b)

Sotrovimab

Date	EUA Letter
2/23/2022	On February 23, 2022, having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the December 16, 2021 letter in its entirety, to further limit the use of sotrovimab when administered for treatment of COVID-19 to exclude geographic regions where, based on available information including variant susceptibility to these drugs and regional variant frequency, infection is likely due to a variant that is non-susceptible to sotrovimab. Corresponding revisions have also been made to the authorized Fact Sheets. The Fact Sheet for Healthcare Providers has also been revised to include updated intravenous infusion times; safety, efficacy, and pharmacokinetic data from the COMET-TAIL clinical trial, and additional information on the susceptibility of SARS-CoV-2 variants to sotrovimab. **Scope of Authorization** • Distribution of the authorized sotrovimab will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. GSK will supply sotrovimab to authorized distributor(s), who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed. • Sotrovimab will be used only by healthcare providers to treat mild-to-moderate COVID-19 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 progression to severe COVID-19, including hospitalization or death. • Sotrovimab is not authorized for use in the following patient populations: o Adults or pediatric patients who are hospitalized due to COVID-19 o Adults or pediatric patients who require oxygen therapy and/or respiratory support due to COVID-19 o Adults or pediatric patients who require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 in those patients on chronic oxygen. • Sotrovimab is not authorized for treatment of mild to moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant, based on available information including variant susceptibility to this drug and regional variant frequency. • Sotrovimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary. • The use of sotrovimab covered by this authorization must be in accordance with the authorized Fact Sheets.
5/26/2021	The FDA issued an EUA on May 26, 2021 for emergency use of sotrovimab for the treatment of mild to moderate coronavirus disease 2019 (COVID-19). (U.S. FDA EUA, 2020f) **Scope of Authorization** • Sotrovimab will be used only by healthcare providers to treat mild-to-moderate COVID-19 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 progression to severe COVID-19, including hospitalization or death; • Sotrovimab is NOT authorized for use in the following patient populations:

Date	EUA Letter
	o Adults or pediatric patients who are hospitalized due to COVID-19, or o Adults or pediatric patients who require oxygen therapy due to COVID-19, or o Adults or pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity. • Sotrovimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary. • The use of sotrovimab covered by this authorization must be in accordance with the authorized Fact Sheets.

Product Description
Sotrovimab is supplied in individual single dose vials. Individual vials and carton container labeling for sotrovimab are clearly marked "For use under Emergency Use Authorization." 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.

Tixagevimab co-packaged with cilgavimab) Evusheld

Date	EUA Letter
2/24/2022	On February 24, 2022, having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2)(C) of the Act, FDA is reissuing the December 20, 2021 letter in its entirety, to include a new condition of authorization on registration and listing. The authorized Fact Sheet for Healthcare Providers and authorized Fact Sheet for Patients, Parents and Caregivers have also been revised to include updated dosing information for Evusheld. **Scope of Authorization** remains unchanged, see below.
12/8/2021	The FDA issued a EUA on December 8, 2021 for emergency use of Tixagevimab co-packaged with cilgavimab) Evusheld 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). (U.S. FDA EUA, 2021) **Scope of Authorization** • Distribution of the authorized Evusheld will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. AstraZeneca will supply Evusheld to authorized distributor(s), who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed; • Evusheld may only be used in adults and pediatric individuals (12 years of age and older weighing at least 40 kg): o 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). <u>Limitations on Authorized Use</u>

Date	EUA Letter
	• Evusheld is **not** authorized for the following uses in individuals: o For treatment of COVID-19, or o For post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2. • Pre-exposure prophylaxis with Evusheld is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended. Individuals for whom COVID-19 vaccination is recommended, including individuals with moderate to severe immune compromise who may derive benefit from COVID-19 vaccination, should receive COVID-19 vaccination. • For individuals who have received a COVID-19 vaccine, Evusheld should be administered at least two weeks after vaccination. • The use of Evusheld covered by this authorization must be in accordance with the authorized Fact Sheets

Product Description
Tixagevimab and cilgavimab, the active components of Evusheld, are neutralizing IgG1 monoclonal antibodies that bind to distinct, non-overlapping epitopes within the receptor binding domain of the spike protein of SARS-CoV-2. Evusheld is an investigational drug and is not approved for any uses, including use as pre-exposure prophylaxis of COVID-19.

Based on the review of the data from the PROVENT clinical trial (NCT04625725), a Phase III randomized, double-blind, placebo-controlled clinical trial, 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, 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.

Tocilizumab (Actemra IV)

Date	EUA Letter
6/24/2021	The FDA issued a EUA on June 24, 2021 for emergency use of Actemra (tocilizumab) IV for the treatment of coronavirus disease 2019 (COVID-19) in certain hospitalized patients. (U.S. FDA EUA, 2020e) **Scope of Authorization** • Actemra will be used only by healthcare providers to treat COVID-19 in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO • Actemra may only be administered via intravenous infusion • The use of Actemra covered by this authorization must be in accordance with the authorized Fact Sheets

Product Description
Actemra is supplied in individual single dose vials. Actemra is a recombinant humanized monoclonal antibody that selectively binds to both soluble and membrane-bound human IL-6 receptors (sIL6R and mIL-6R) and subsequently inhibits IL-6-mediated signaling through these receptors.

Actemra injection is a preservative-free, sterile clear, colorless to pale yellow solution. The authorized product includes commercially available7 Actemra, which is supplied as 80 mg/4 mL (NDC 50242-135-01), 200 mg/10 mL (NDC 50242-136-01), and 400 mg/20 mL (NDC 50242-137-01) individually packaged 20 mg/mL single-dose vials for further dilution prior to intravenous infusion.

REVOKED EUA(s)

Bamlanivimab

Date	EUA Letter
4/16/2021	The FDA revoked the EUA for bamlanivimab on April 16, 2021 that allowed for the investigational monoclonal antibody therapy bamlanivimab, *when administered alone*, to be used for the treatment of mild-to-moderate COVID-19 in adults and certain pediatric patients. Based on its ongoing analysis of emerging scientific data, specifically the sustained increase of SARS-CoV-2 viral variants that are resistant to bamlanivimab alone resulting in the increased risk for treatment failure, the FDA has determined that the known and potential benefits of bamlanivimab, when administered alone, no longer outweigh the known and potential risks for its authorized use. Therefore, the agency determined that the criteria for issuance of an authorization are no longer met and has revoked the EUA. (U.S. FDA EUA, 2021d)
2/9/2021	The FDA re-issued the EUA for bamlanivimab on February 9, 2021. Its scope of authorization remains unchanged (see below); updates were made to corresponding Fact Sheets regarding reporting requirements, dose preparation and administration changes, and update of warnings or side-effects. (U.S. FDA EUA, 2021d)
11/9/2020	The FDA issued a EUA on November 11, 2020 to permit the emergency use of the unapproved product, bamlanivimab. Bamlanivimab is a neutralizing IgG1 monoclonal antibody that binds to the receptor binding domain of the spike protein of SARS-CoV-2. (U.S. FDA EUA, 2020d) It is an investigational drug and is not currently approved for any indication. Scope of Authorization: • Distribution of the authorized bamlanivimab will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Lilly will supply bamlanivimab to authorized distributors, who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities, as needed; • The bamlanivimab covered by this authorization will be used only by healthcare providers to treat mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization; • Bamlanivimab is not authorized for use in the following patient populations: o Adults or pediatric patients who are hospitalized due to COVID-19, or o Adults or pediatric patients who require oxygen therapy due to COVID19, or o Adults or pediatric patients who require an increase in baseline oxygen Flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity • Bamlanivimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary • The use of bamlanivimab covered by this authorization must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets.

Chloroquine phosphate, hydroxychloroquine sulfate

Date	EUA Letter
6/15/2020	The FDA revoked the EUA that allowed for chloroquine phosphate and hydroxychloroquine sulfate on June 15, 2020... The agency determined that the legal criteria for issuing a EUA are no longer met. Based on its ongoing analysis of the EUA and emerging scientific data, the FDA determined that chloroquine and hydroxychloroquine are unlikely to be effective in treating COVID-19 for the authorized uses in the EUA. Additionally, in light of ongoing serious cardiac adverse events and other potential serious side effects, the known and potential benefits of chloroquine and hydroxychloroquine no longer outweigh the known and potential risks for the authorized use.(U.S. FDA EUA, 2020a)

Coding

Note: Drugs and biologics are typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions.

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J0248	Injection, remdesivir, 1 mg
J3490†	Unclassified drugs
M0220	Injection, tixagevimab and cilgavimab, for the pre-exposure prophylaxis only, for certain adults and pediatric individuals (12 years of age and older weighing at least 40kg) with no known sars-cov-2 exposure, who either have moderate to severely compromised immune systems or for whom vaccination with any available covid-19 vaccine is not recommended due to a history of severe adverse reaction to a covid-19 vaccine(s) and/or covid-19 vaccine component(s), includes injection and post administration monitoring
M0221	Injection, tixagevimab and cilgavimab, for the pre-exposure prophylaxis only, for certain adults and pediatric individuals (12 years of age and older weighing at least 40kg) with no known sars-cov-2 exposure, who either have moderate to severely compromised immune systems or for whom vaccination with any available covid-19 vaccine is not recommended due to a history of severe adverse reaction to a covid-19 vaccine(s) and/or covid-19 vaccine component(s), includes injection and post administration monitoring in the home or residence; this includes a beneficiary's home that has been made provider-based to the hospital during the covid-19 public health emergency
M0222	Intravenous injection, bebtelovimab, includes injection and post administration monitoring
M0223	Intravenous injection, bebtelovimab, includes injection and post administration monitoring in the home or residence; this includes a beneficiary's home that has been made provider-based to the hospital during the COVID-19 public health emergency
M0249	Intravenous infusion, tocilizumab, for hospitalized adults and pediatric patients (2 years of age and older) with covid-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) only, includes infusion and post administration monitoring, first dose
M0250	Intravenous infusion, tocilizumab, for hospitalized adults and pediatric patients (2 years of age and older) with covid-19 who are receiving systemic corticosteroids and require

HCPCS Codes	Description
	supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) only, includes infusion and post administration monitoring, second dose
Q0220	Injection, tixagevimab and cilgavimab, for the pre-exposure prophylaxis only, for certain adults and pediatric individuals (12 years of age and older weighing at least 40kg) with no known sars-cov-2 exposure, who either have moderate to severely compromised immune systems or for whom vaccination with any available covid-19 vaccine is not recommended due to a history of severe adverse reaction to a covid-19 vaccine(s) and/or covid-19 vaccine component(s), 300 mg
Q0222	Injection, bebtelovimab, 175 mg
Q0249	Injection, tocilizumab, for hospitalized adults and pediatric patients (2 years of age and older) with covid-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) only, 1 mg

†**Note: Considered Medically Necessary when used to casirivimab and imdevimab (REGEN-COV) 300mg.**

Considered Experimental/Investigational/Unproven:

HCPCS Codes	Description
M0239	Intravenous infusion, bamlanivimab-xxxx, includes infusion and post administration monitoring [effective 4/16/2021]
M0240	Intravenous infusion or subcutaneous injection, casirivimab and imdevimab includes infusion or injection, and post administration monitoring, subsequent repeat doses [effective 01/24/2022]
M0241	Intravenous infusion or subcutaneous injection, casirivimab and imdevimab includes infusion or injection, and post administration monitoring in the home or residence, this includes a beneficiary's home that has been made provider-based to the hospital during the covid-19 public health emergency, subsequent repeat doses [effective 01/24/2022]
M0243	Intravenous infusion, casirivimab and imdevimab includes infusion and post administration monitoring [effective 01/24/2022]
M0244	Intravenous infusion or subcutaneous injection, casirivimab and imdevimab includes infusion or injection, and post administration monitoring in the home or residence; this includes a beneficiary's home that has been made provider-based to the hospital during the covid-19 public health emergency [effective 01/24/2022]
M0245	Intravenous infusion, bamlanivimab and etesevimab, includes infusion and post administration monitoring [effective 01/24/2022]
M0246	Intravenous infusion, bamlanivimab and etesevimab, includes infusion and post administration monitoring in the home or residence; this includes a beneficiary's home that has been made provider-based to the hospital during the covid-19 public health emergency [effective 01/24/2022]
M0247	Intravenous infusion, sotrovimab, includes infusion and post administration monitoring [effective 04/05/2022]
M0248	Intravenous infusion, sotrovimab, includes infusion and post administration monitoring in the home or residence; this includes a beneficiary's home that has been made provider-based to the hospital during the covid-19 public health emergency [effective 04/05/2022]
Q0239	Injection, bamlanivimab-xxxx, 700 mg
Q0240	Injection, casirivimab and imdevimab, 600 mg [effective 01/24/2022]
Q0243	Injection, casirivimab and imdevimab, 2400 mg [effective 01/24/2022]
Q0244	Injection, casirivimab and imdevimab, 1200 mg [effective 01/24/2022]
Q0245	Injection, bamlanivimab and etesevimab, 2100 mg [effective 01/24/2022]
Q0247	Injection, sotrovimab, 500 mg [effective 04/05/2022]

ICD-10-CM Diagnosis Codes	Description
	All diagnosis codes

General Background

FDA-Approved Indication

Drug	FDA-approved Indication
Remdesivir (Veklury®)	Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are: • Hospitalized, or • Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

FDA Prescribing Information

Drug	Prescribing Information
Baricitinib (Olumiant)	Olumiant is indicated for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). Dosage The recommended dosage of Olumiant for adults is 4 mg once daily orally, with or without food, for 14 days or until hospital discharge, whichever occurs first. An alternative administration for patients unable to swallow tablets may be used. Alternative Administration for Patients Unable to Swallow Tablets For patients who are unable to swallow whole tablets, an alternative mode of administration may be considered: • Oral dispersion • Gastrostomy tube (G tube) • Nasogastric tube (NG tube) or orogastric tube (OG tube) Intact tablets are not hazardous. Tablets may be crushed to facilitate dispersion.
Remdesivir (Veklury®)	Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are: • Hospitalized, or • Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death. Dosage **Recommended Dosage in Adults and Pediatric Patients 12 Years of Age and Older and Weighing at Least 40 kg** The recommended dosage for adults and pediatric patients 12 years of age and older and weighing at least 40 kg is a single loading dose of Veklury 200 mg on Day

	1 via intravenous infusion followed by once-daily maintenance doses of Veklury 100 mg from Day 2 via intravenous infusion. Hospitalized patients: The treatment course of Veklury should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made. • The recommended total treatment duration for hospitalized patients requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) is 10 days. • The recommended treatment duration for hospitalized patients not requiring invasive mechanical ventilation and/or ECMO is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days for a total treatment duration of up to 10 days. Non-hospitalized patients: The treatment course of Veklury should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made and within 7 days of symptom onset. • The recommended total treatment duration for non-hospitalized patients diagnosed with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, is 3 days. Product Availability Veklury is available in two dosage forms: • Veklury for injection, 100 mg, available as a sterile, preservative-free white to off-white to yellow lyophilized powder in single-dose vial for reconstitution. • Veklury injection, 100 mg/20 mL (5 mg/mL), available as a clear, colorless to yellow solution, free of visible particles in single-dose vial. Other • Risk of Reduced Antiviral Activity When Coadministered with Chloroquine Phosphate or Hydroxychloroquine Sulfate o Coadministration of Veklury and chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on cell culture data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of Veklury • **Pediatric Use** o The safety and effectiveness of Veklury for the treatment of COVID-19 have been established in pediatric patients 12 years and older and weighing at least 40 kg, who are: ▪ Hospitalized, or ▪ Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death. o The safety and effectiveness of Veklury have not been established in pediatric patients younger than 12 years of age or weighing less than 40 kg.

Disease Overview

Coronavirus disease 2019 (COVID-19) is a respiratory illness that can spread from person-to-person. Many types of human coronaviruses exist, including some that commonly cause mild upper-respiratory tract illnesses. COVID-19 is a new disease, caused by a novel (new) coronavirus that has not previously been seen in humans. Current symptoms reported for patients with COVID-19 have included mild to severe respiratory illness with fever, cough, and difficulty breathing. (FDA FAQs, 2020)

National Institute of Health (NIH) COVID-19 Treatment Guidelines - Clinical Spectrum of SARS-CoV-2 Infection

In general, adults with SARS-CoV-2 infection can be grouped into the following severity of illness categories:

- **Asymptomatic or Presymptomatic Infection**: Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test [NAAT] or an antigen test) but who have no symptoms that are consistent with COVID-19.

- **Mild Illness**
  - Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging
  - Or the absence of viral pneumonia ad hypoxemia, can be managed in ambulatory care setting or at home

- **Moderate Illness**
  - Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO_2) ≥94% on room air at sea level.
  - Or those individuals with viral pneumonia, but without hypoxemia

- **Severe Illness**: Individuals who have SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%.

- **Critical Illness:** Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction. (NIH, 2021)

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Policy Update History

Summary of Changes (1/1/2021 - Present)	Date
Important **change** in coverage criteria: • Added criteria for Bamlanivimab-Etesevimab consistent with the Emergency Use Authorization issued on 2/9/2021	3/4/2021
Update to the Health Care Provider Fact Sheets regarding antiviral resistance information for the following products: bamlanivimab, bamlanivimab-etesevimab, and casirivimab-imdevimab.	4/8/2021
Important **change** in coverage criteria: • Removed bamlanivimab monotherapy criteria as its Emergency Use Authorization was revoked on 4/16/2021	4/23/2021
Important **changes** in coverage criteria: • Added criteria for Sotrovimab consistent with Emergency Use Authorization on 5/26/2021 • Updated "high risk" definition for Bamlanivimab-Estesevimab, Casirivimab-Imdevimab (REGEN-COV)	6/8/2021
Important **change** in coverage criteria: • Added criteria for tocilizumab (Actemra) intravenous consistent with Emergency Use Authorization issued on 6/24/2021 • Added Emergency Use Authorization letter re-issued on 6/25/2021 for the combination of Bamlanivimab and Estesevimab regarding pause on all distribution of the product	7/6/2021
Important **changes** in coverage criteria: • Modified baricitinib's (Olumiant) criteria consistent with the most recent Emergency Use Authorization issued on 7/28/2021 • Modified casirivimab-imdevimab (REGEN-COV) criteria consistent with the most recent Emergency Use Authorization on 7/30/2021 for Post-Exposure Prophylaxis	8/3/2021
Important **changes** in coverage criteria: • Modified bamlanivimab-etesevimab criteria consistent with the most recent Emergency Use Authorization issued on 8/27/2021 for resumption of distribution only in states, territories, and U.S.	8/31/2021

Summary of Changes (1/1/2021 - Present)	Date
jurisdictions in which recent data shows the combined frequency of variants resistant to bamlanivimab and etesevimab administered together is less than or equal to 5%	
Important **changes** in coverage criteria: • Modified bamlanivimab-etesevimab criteria consistent with the most recent Emergency Use Authorization issued on 9/16/2021 for Post-Exposure Prophylaxis	9/28/21
Important **changes** in coverage criteria: • Added criteria for tofacitinib (Xeljanz/Xeljanz XR) consistent with treatment guidelines • Added criteria for sarilumab (Kevzara) consistent with treatment guidelines • Added concurrent use of interleukin-6 blockers and janus kinase inhibitors as a condition not covered	11/9/2021
Important **changes** in coverage criteria: • Modified bamlanivimab-etesevimab criteria consistent with the most recent Emergency Use Authorization issued on 12/3/2021 that expanded Treatment and Post-Exposure Prophylaxis uses down to neonates	12/9/2021
Important **changes** in coverage criteria: • Added criteria for Evusheld (cilgavimab and tixagevimab) consistent with Emergency Use Authorization issued on 12/8/2021 for use as Pre-Exposure Prophylaxis of COVID-19 in certain adults and pediatric individuals	12/21/2021
Important **changes** in coverage criteria: • Added criteria for Paxlovid (nirmatrelvir-ritonavir) consistent with Emergency Use Authorization issued on 12/22/2021 for use as Treatment of mild-to-moderate COVID-19 in certain adults and pediatric individuals • Added criteria for molnupiravir consistent with Emergency Use Authorization issued on 12/23/2021 for use as Treatment of mild-to-moderate COVID-19 in certain adults when other alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate • Added criteria for remdesivir to expand to out-patient use consistent with treatment guidelines	1/4/2022
Important **changes** in coverage criteria: • Modified remdesivir (Veklury) criteria consistent with the most recent Emergency Use Authorization issued January 21, 2022 and FDA label update that expanded for use in the outpatient setting • Modified bamlanivimab-etesevimab and REGEN-COV criteria consistent with the most recent Emergency Use Authorization and Health Care Provider Fact Sheet issued on January 21, 2022 that prohibits use of these products in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant	1/21/2022
Important **changes** in coverage criteria: • Added criteria for bebtelovimab consistent with Emergency Use Authorization issued on 2/11/2022 for use as Treatment of mild-to-moderate COVID-19 in certain adults and pediatric individuals	2/15/2022
Important **changes** in coverage criteria: • Added criteria for Sotrovimab consistent with Emergency Use Authorization on 2/23/202 • Updated Evusheld dosing consistent with Health Care Provider Fact Sheet update on 2/24/2022	3/3/2022
Important **changes** in coverage criteria: • Updated Evusheld dosing consistent with Health Care Provider Fact Sheet update on 4/1/2022 • Added criteria for intravenous immunoglobulin for use in the treatment of Multisystem Inflammatory Syndrome in Children (MIS-C) • Added criteria for anakinra for use in the treatment of Refractory Multisystem Inflammatory Syndrome in Children (MIS-C) • Added criteria for infliximab for use in the treatment of Refractory Multisystem Inflammatory Syndrome in Children (MIS-C) • Updated non-susceptibility non-coverage criteria for: Bamlanivimab-Estesevimab, REGEN-COV, Sotrovimab	4/12/2022
Important **changes** in coverage criteria: • Modified and relocated baricitinib (Olumiant) criteria secondary to FDA-approval for use in the treatment of COVID-19 in adults on May 10, 2022; baricitinib's existing EUA modified for treatment of COVID-19 to 2 to less than 18 years of age accordingly	5/19/2022
Update to the Health Care Provider Fact Sheet regarding repeat dosing for cilgavimab and tixagevimab (Evusheld).	7/28/2022
Minor **changes** in coverage criteria: • Updated bebtelovimab and molnupiravir alternative COVID-19 treatment option example list secondary to remdesivir and sotrovimab no longer being recommended prior to their use due the following: may not be feasible or practical for certain patients (remdesivir), current variant resistance patterns resulting in pauses of distribution of product (sotrovimab)	8/16/2022