Drug and Biologic Coverage Policy

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COVID-19 Drug and Biologic Therapeutics

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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. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. 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.

Products addressed in this policy include:

- Gohibic (vilobelimab)
- Infliximab
- Intravenous Immunoglobulin (IVIG)
- Lagevrio™ (molnupiravir)
- Pemgarda™ (pemivibart)

Agents with Withdrawn Emergency Use Authorization (EUA):

- Bamlanivimab and Etesevimab [1/24/2022]
- Bebtelovimab [11/30/2022]
- Casirivimab and Imdevimab (REGEN-COV™) [1/24/2022]
- Sotrovimab [4/5/2022]
- Tixagevimab and Cilgavimab (Evusheld™) [1/26/2023]

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 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).

Medical Necessity Criteria

Product-specific coverage criteria for Drugs or Biologics used for the treatment, prevention, or management of COVID-19 and related symptoms are listed in below table:

Product	Medical Necessity Criteria
Gohibic (vilobelimab)	**Gohibic is considered medically necessary when the following criteria are met (1):** 1. **COVID-19 – Hospitalized.** Patient meets **ALL** of the following (A, B, C, D, and E): A. 18 years of age or older B. Hospitalized with a diagnosis of COVID-19 with positive results from direct SARS-CoV-2 viral testing (for example, molecular [PCR], or antigen [ELISA] laboratory methods) C. Requires invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO) D. Is administered within 48 hours of receiving IMV or ECMO E. Gohibic must be use in accordance with the authorized Health Care Provider Fact Sheets **Any other use is considered not medically necessary.**
Infliximab	**Infliximab is considered medically necessary when the following criteria are met (1):** 1. **COVID-19 Associated Refractory Multisystem Inflammatory Syndrome in Children (MIS-C).** Patient meets **ALL** of the following (A, B, C, D, and E): A. 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. 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, at least **ONE** 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 not be used in combination with anakinra **Dosing**. Up to 5 - 10 mg/kg intravenous (IV) **given one time**. **Any other use in the management of COVID-19 is considered not medically necessary.**
Intravenous Immunoglobulin (IVIG)	**Intravenous immunoglobulin (IVIG) is considered medically necessary when the following criteria are met (1):** **1. COVID-19 Associated Multisystem Inflammatory Syndrome in Children (MIS-C).** Patient meets **ALL** of the following (A, B, C, D, E and F): A. 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 or ii): 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. Has **ALL** of the following symptoms and laboratory findings (i, ii, and iii): 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, at least **ONE** 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., greater than 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 **Dosing**. Up to 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). **Any other use in the management of COVID-19 is considered not medically necessary.**
Lagevrio™ (molnupiravir)	**Lagevrio is considered medically necessary when the following criteria are met (1):** 1. **COVID-19**. Patient meets **ONE** of the following (A or B): A. Initial Therapy. **ALL** of the following (i, ii, iii, iv and v): i. Diagnosis 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. 18 years of age or older iii. At high risk for progressing to severe COVID-19

Note: 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 high 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/m^2, 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

iv. Alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate (for example, Paxlovid)

v. Molnupiravir must be in accordance with the authorized Health Care Provider Fact Sheets

B. Previously received molnupiravir, then **ALL** of the following (i, ii, iii and iv):

i. 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)

ii. This is a second diagnosis unrelated to the initial diagnosis of COVID-19 treated with molnupiravir.

iii. At least 90 days have elapsed since completion of the initial course of molnupiravir for treatment of COVID-19

iv. Alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate (for example, Paxlovid)

Authorization is for one course of treatment (40 capsules) for a duration of 5 days.

Any other use is considered not medically necessary, including the following (this list may not be all inclusive):

1. **Less than 18 years of age.**
2. **Initiation of treatment in patient requiring hospitalization due to COVID-19.** Patient 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. 3. **Pre-Exposure or Post-Exposure Prophylaxis for prevention of COVID-19.** 4. **For use longer than 5 consecutive days.**
Pemgarda (pemivibart)	**Pemgarda is considered medically necessary when the following criteria are met (1):** **1. Pre-exposure Prophylaxis of Coronavirus Disease 2019 (COVID-19).** Approve for 1 month if the patient meets **ALL** of the following (A, B,C <u>and</u> D): A. Is ≥ 12 years of age B. Is ≥ 40 kg (88 lbs) C. According to the prescriber, patient is currently <u>not</u> infected with SARS-CoV-2 and has <u>not</u> had a known recent exposure to a patient infected with SARS-CoV-2 D. According to the prescriber, patient has moderate-to-severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and is unlikely to mount an adequate immune response to COVID-19 vaccination <u>Note</u>: Medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination include: active treatment for solid tumor and hematologic malignancies; hematologic malignancies associated with poor responses to COVID-19 vaccines regardless of current treatment status (e.g., chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, acute leukemia); receipt of solid-organ transplant or an islet 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 immunosuppressive therapy); moderate or severe primary immunodeficiency (e.g., common variable immunodeficiency disease, severe combined immunodeficiency, 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, and biologic agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents) **Dosing**. Approve a single 4,500 mg dose administered intravenous (IV) infusion, not more frequently than once every 3 months. **Any other use is considered not medically necessary, including the following** (this list may not be all inclusive)**:** 1. **For treatment of COVID-19.** Limitation of authorized use per the FDA. 2. **For post-exposure prophylaxis of COVID-19 in patients who have been exposed to someone infected with SARS-CoV-2.** Limitation of authorized use per the FDA. 3. **Pre-exposure prophylaxis vaccine substitution in patients for whom COVID-19 vaccination is recommended.** Limitation of authorized use per the FDA; Pre-exposure prophylaxis with Pemgarda is <u>not</u> a substitute for vaccination in patients for whom COVID-19 vaccination is recommended. Patients for whom COVID-19

	vaccination is recommended, including patients with moderate-to-severe immune compromise who may derive benefit from COVID-19 vaccination, should receive COVID-19 vaccination. 4. **Pemgarda administered < 2 weeks after COVID-19 vaccination.** Limitation of authorized use per the FDA; in patients who have recently received a COVID-19 vaccine, Pemgarda should be administered at least 2 weeks after vaccination.

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.

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

Coding Information

Drugs 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
M0224	Intravenous infusion, pemivibart, for the pre-exposure prophylaxis only, for certain adults and adolescents (12 years of age and older weighing at least 40 kg) with no known SARS-CoV-2 exposure, who either have moderate-to-severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments, includes infusion and post administration monitoring [effective 3/22/2024]
Q0224	Injection, pemivibart, for the pre-exposure prophylaxis only, for certain adults and adolescents (12 years of age and older weighing at least 40 kg) with no known SARS-CoV-2 exposure, and who either have moderate-to-severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments, and are unlikely to mount an adequate immune response to COVID-19 vaccination, 4500 mg [effective 3/22/2024]

Considered Experimental/Investigational/Unproven:

HCPCS Codes	Description
J3490†	Unclassified drugs [effective 01/24/2022]
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 [effective 01/26/2023]
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

HCPCS Codes	Description
	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 [effective 01/26/2023]
M0222	Intravenous injection, bebtelovimab, includes injection and post administration monitoring [effective 11/30/2022]
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 [effective 11/30/2022]
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 until 06/30/2025]
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 [effective 01/26/2023]
Q0222	Injection, bebtelovimab, 175 mg [effective 11/30/2022]
Q0239	Injection, bamlanivimab-xxxx, 700 mg [effective 4/16/2021]
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]

†Note: Considered Experimental/Investigational/Unproven when used to report casirivimab and imdevimab (REGEN-COV) 300mg.

ICD-10-CM Diagnosis Codes	Description
	All diagnosis codes

General Background

FDA Prescribing Information

Drug	Prescribing Information
Gohibic (vilobelimab)	**EMERGENCY USE AUTHORIZATION FOR GOHIBIC** The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of GOHIBIC for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults when initiated within 48 hours of receiving invasive mechanical ventilation (IMV), or extracorporeal membrane oxygenation (ECMO). However, Gohibic is not FDA-approved for this use.[47] **Dosage and Administration[47]** Recommended Dosage The recommended dosage of GOHIBIC for the treatment of adults with COVID-19 is 800 mg administered by intravenous infusion after dilution for a maximum of 6 (six) doses over the treatment period as described below. Treatment should be started within 48 hours of intubation (Day 1) followed by administration on Days 2, 4, 8, 15 and 22 as long as the patient is hospitalized (even if discharged from ICU). Administration • Administer diluted GOHIBIC via intravenous infusion over 30 – 60 minutes. **Dosage Forms and Strengths[47]** • Injection: 200 mg/20 mL (10 mg/mL) in single-dose vials for further dilution.
Molnupiravir (Lagevrio)[14]	**EMERGENCY USE AUTHORIZATION FOR LAGEVRIO** 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
Pemgarda[46]	**EMERGENCY USE AUTHORIZATION FOR PEMGARDA** The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product Pemgarda (pemivibart) for the pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in adults and adolescents (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 • Who have moderate-to-severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and are unlikely to mount an adequate response to COVID-19 vaccination. • Medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination include: o Active treatment for solid tumor and hematologic malignancies o Hematologic malignancies associated with poor responses to COVID-19 vaccines regardless of current treatment status (e.g., chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, acute leukemia) o Receipt of solid-organ transplant or an islet 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 immunosuppressive therapy) ○ Moderate or severe primary immunodeficiency (e.g., common variable immunodeficiency disease, severe combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome) ○ Advanced or untreated HIV infection (people with HIV and CD4 cell counts <200/mm3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV) ○ Active treatment with high-dose corticosteroids (i.e., ≥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, and biologic agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents) **Limitations of Authorized Use** • Pemgarda is not authorized for use: ○ For treatment of COVID-19, or ○ For post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2. • Pemgarda is authorized for use only when the combined national frequency of variants with substantially reduced susceptibility to Pemgarda is less than or equal to 90%, based on available information including variant susceptibility to Pemgarda and national variant frequencies1 . • Pre-exposure prophylaxis with Pemgarda 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. • In individuals who have recently received a COVID-19 vaccine, Pemgarda should be administered at least 2 weeks after vaccination. Pemgarda 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. **Dosage and Administration** <u>Initial Dosing:</u> The initial dosage of PEMGARDA in adults and adolescents (12 years of age and older weighing at least 40 kg) is 4,500 mg administered as a single intravenous (IV) infusion. <u>Repeat Dose:</u> The repeat dosage is 4,500 mg of Pemgarda administered as a single IV infusion every 3 months. Repeat dosing should be timed from the date of the most recent Pemgarda dose. The recommendations for dosing are based on the totality of the scientific evidence including clinical pharmacology data, antiviral activity data, and clinical study data. <u>Dosage Adjustment in Specific Populations</u> No dosage adjustment is recommended in pregnant or lactating individuals, in geriatrics, or in individuals with renal or hepatic impairment. **Dosage Forms and Strengths** • Injection: 500 mg/4 mL (125 mg/mL) in a single-dose vial

Other Uses with Supportive Evidence

Multisystem Inflammatory Syndrome in Children (including refractory disease): 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 <u>not</u> 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).

<u>Guideline Evidence Rating Scales</u>

Infectious Diseases Society of America Evidence Rating[3]

- 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[4]

- 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[39]

- 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

Active FDA Emergency Use Authorizations

Gohibic (vilobelimab)

Date	EUA Letter
4/12/2023	Re-issued.[48]
4/4/2023	The FDA issued a EUA on April 4, 2023, for emergency use of Gohibic (vilobelimab) for the treatment of COVID-19 in hospitalized adults when initiated within 48 hours of receiving IMV, or ECMO.[48]

Lagevrio (molnupiravir)

Date	EUA Letter
11/15/2023	Re-issued.[14]
10/27/2022	Re-issued.[14]
8/5/2022	Re-issued.[14]
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.[14]

Pemgarda (pemivibart)

Date	EUA Letter
8/26/2024	Re-issued.[47]
3/22/2024	On March 22, 2024, the FDA issued an emergency use authorization for Pemgarda for pre-exposure prophylaxis of COVID-19 in adults and adolescents (12 years of age and older weighing at least 40kg).[47]

Withdrawn FDA Emergency Use Authorizations

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.[9]

Bamlanivimab and Etesevimab

Date	EUA Letter
1/24/2022	As of **1/24/2022,** 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 Bamlanivimab and Etesevimab 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. [45]

Bebtelovimab

Date	EUA Letter
11/30/2022	As of **11/30/2022,** the Centers for Disease Control and Prevention (CDC) estimated the proportion of COVID-19 cases to be caused by the Omicron subvariant BQ.1 and BQ.1.1to be above 50% in all U.S. Department of Health and Human Services (HHS) regions. **Due to these data, use of bebtelovimab 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 bebtelovimab distribution to all U.S. states and territories. The FDA has updated the Fact Sheet for bebtelovimab to reflect product use restrictions. [45]

Casirivimab and Imdevimab (REGEN-COV)

Date	EUA Letter
1/24/2022	As of **1/24/2022,** 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 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. [45]

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.[33]

Sotrovimab

Date	EUA Letter
4/5/2022	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. [45]

Tixagevimab co-packaged with cilgavimab) Evusheld

Date	EUA Letter
1/26/2023	January 26, 2023: FDA reissued the December 8, 2022, letter in its entirety, to revise the scope of authorization to limit the use of Evusheld for pre-exposure prophylaxis of COVID-19 in the United States only when, based on available information including variant susceptibility to EVUSHELD and national variant frequencies, the combined frequency of non-susceptible variants nationally is less than or equal to 90%.[31] Data show Evusheld is unlikely to be active against certain SARS-CoV-2 variants. According to the most recent CDC Nowcast data, these variants are projected to be responsible for more than 90% of current infections in the U.S. This means that Evusheld is not expected to provide protection against developing COVID-19 if exposed to those variants. **Accordingly, Evusheld is NOT currently authorized in any U.S. region due to the high frequency of circulating SARS-CoV-2 variants that are non-susceptible to Evusheld.** Therefore, Evusheld may not be administered for pre-exposure prophylaxis for prevention of COVID-19 under the Emergency Use Authorization until further notice by the Agency.[31]

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.[2]

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[4]:

- **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.

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Revision Details

Summary of Changes	Date
Important changes in coverage criteria: • **Added** criteria for anakinra consistent with Emergency Use Authorization issued on 11/8/2022 for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR)	11/17/2022
Important changes in coverage criteria: • **Removed** coverage criteria for bebtelovimab secondary to Emergency Use Authorization withdrawal issued on 11/30/2022	12/6/2022
Important changes in coverage criteria: • **Updated** and relocated tocilizumab intravenous (Actemra IV) criteria secondary to FDA-approval for use in the treatment of COVID-19 in adults on December 21, 2022; tocilizumab's existing EUA modified for treatment of COVID-19 to 2 to less than 18 years of age accordingly	1/17/2023
Important changes in coverage criteria: • **Removed** coverage criteria for tixagevimab co-packaged with cilgavimab (Evusheld) secondary to Emergency Use Authorization withdrawal issued on 1/26/2023	1/31/2023

Important changes in coverage criteria: • **Added** criteria for vilobelimab consistent with Emergency Use Authorization issued on 4/4/2023 for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults when initiated within 48 hours of receiving IMV, or ECMO • **Removed** Regiocit criteria, and placed in Unassigned Drug or Biologic Code Medical Precertification coverage policy (1701)	4/25/2023
Important changes in coverage criteria: • Paxlovid tablets and Lagevrio capsules: **updated** Override criteria to require at least 90 days to have elapsed since completion of the initial course of treatment for COVID-19. Previously, criteria required at least 120 days to have elapsed.	11/24/2023
Important changes in coverage criteria: • **Removed** Paxlovid tablets from the policy.	5/1/2024
Important changes in coverage criteria: • **Removed** Veklury (remdesivir) and Kineret from the policy	6/15/2024
Important changes in coverage criteria: • **Removed** Tocilizumab intravenous, Kevzara, Olumiant, and Xeljanz/Xeljanz medical necessity criteria from the policy.	11/01/2024
Important changes in coverage criteria: • **Added** Pemgarda (pemivibart) coverage criteria consistent with Emergency Use Authorization issued on 8/26/2024 for use as pre-exposure prophylaxis of COVID-19 in certain adults and adolescents **Coding Information** **Updated** Coding**:** • **Added:** M0224 (effective 3/22/2024), Q0224 (effective 3/22/2024)	11/14/2024
Coding Information: • Updated the description for HCPCS M0248 to include the note “effective until 6/30/2025”	6/1/2025

The policy effective date is in force until updated or retired.