Drug and Biologic Coverage Policy

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COVID-19 Drug and Biologic Therapeutics

Table of Contents

Overview 1
Medical Necessity Criteria 2
Coding Information 9
General Background.....11
References 29
Policy Update History 32

Related Coverage Resources

Anakinra - (IP0243)
Clinical Trials - (A003)
COVID-19: In Vitro Diagnostic Testing - (0557)
Baricitinib - (IP0225)
Infliximab - (IP0242)
Immune Globulins Therapy - (5026)
Ivermectin - (IP0300)
Tocilizumab Intravenous - (IP0228)
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®)
- Baricitinib (Olumiant®)
- Gohibic (vilobelimab)
- Infliximab
- Intravenous Immunoglobulin (IVIG)
- Molnupiravir (Lagevrio™)
- Nirmatrelvir and Ritonavir (Paxlovid™)
- Remdesivir (Veklury®)
- Sarilumab (Kevzara®)
- Tocilizumab intravenous (Actemra IV®)
- Tofacitinib (Xeljanz®/Xeljanz XR®)

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

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 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
Anakinra (Kineret)	**ONE** of the following: **1. COVID-19.** Individual meets **ALL** of the following: 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. Has pneumonia requiring supplemental oxygen (low- or high-flow oxygen) D. Is at risk of progressing to severe respiratory failure E. Is suspected to have elevated (at least 6 ng/mL) plasma soluble urokinase plasminogen activator receptor (suPAR) by having **THREE** of the following: i. 75 years of age or older ii. Severe pneumonia per WHO criteria WHO criteria: Fever or suspected respiratory infection, plus **ONE** of the following: respiratory rate greater than 30 breaths/min, severe respiratory distress; or SpO2 less than or equal to 93% on room air. iii. Current or previous smoker iv. Sequential Organ Failure Assessment (SOFA) score of at least 3 v. Neutrophil-to-lymphocyte ratio (NLR) of at least 7 vi. Hemoglobin less than or equal to 10.5 g/dL vii. History of ischemic stroke

	viii. Blood urea at least 50 mg/dL OR history of renal disease F. Use of Kineret must be in accordance with the authorized Health Care Provider Fact Sheets **Dosing.** Meets **ONE** of the following regimens: A. 100 mg as a subcutaneous injection up to once a day for 10 days B. If renally impaired, 100 mg as a subcutaneous injection every other day for a total of 5 doses over 10 days **2. COVID-19 Associated Refractory Multisystem Inflammatory Syndrome in Children (MIS-C).** Individual meets **ALL** of the following are met: 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 iii. Continues to display the following symptoms and laboratory findings despite intravenous immunoglobulin (IVIG) and glucocorticoid therapy: iv. Fever (> 100.4°F for ≥24 hours, or report of subjective fever lasting ≥ 24 hours) v. 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 vi. Evidence of clinically severe illness that requires hospitalization with multisystem (i.e., > 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological) vii. Other causes have been excluded viii. Anakinra will not be used in combination with infliximab **Dosing.** Up to 5 - 10 mg/kg intravenous (IV), or subcutaneous (SC), in 1 to 4 divided doses administered daily up to 2 weeks. **Any other use in the management of COVID-19 is considered experimental, investigational or unproven.**
Baricitinib (Olumiant®)	**COVID-19 - Hospitalized.** Individual meets **ALL** of the following: 1. 2 years of age or older 2. Treatment of suspected, or laboratory confirmed, COVID-19 3. Is hospitalized requiring supplemental oxygen, invasive mechanical ventilation, or ECMO 4. Use is for a maximum of 14 days or until discharge from the hospital, whichever comes first *Baricitinib may be administered with or without remdesivir.* **Any other use in the management of COVID-19 is considered experimental, investigational or unproven, including the following (this list may not be exhaustive):** **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.[3,4]

Gohibic (vilobelimab)	**COVID-19 – Hospitalized.** Individual meets **ALL** of the following: 1. 18 years of age or older 2. 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) 3. Requires invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO) 4. Is administered within 48 hours of receiving IMV or ECMO 5. Gohibic must be use in accordance with the authorized Health Care Provider Fact Sheets **Any other use is considered experimental, investigational or unproven.**
Infliximab	**COVID-19 Associated Refractory Multisystem Inflammatory Syndrome in Children (MIS-C).** Individual meets **ALL** of the following: 1. Less than 21 years of age 2. **EITHER** of the following: A. Positive for current or recent SARS-CoV-2 infection by molecular [PCR], antigen [ELISA] laboratory methods), or serology results B. COVID-19 exposure within the 4 weeks prior to onset of symptoms 3. Continues to display the following symptoms and laboratory findings despite intravenous immunoglobulin (IVIG) and glucocorticoid therapy: A. Fever (> 100.4°F for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours) B. 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. C. Evidence of clinically severe illness that requires hospitalization with multisystem (i.e., > 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological) 4. Other causes have been excluded 5. Infliximab will <u>not</u> be used in combination with anakinra <u>**Dosing**</u>. Up to 5 - 10 mg/kg intravenous (IV) <u>**given one time**</u>. **Any other use in the management of COVID-19 is considered experimental, investigational or unproven.**
Intravenous Immunoglobulin (IVIG)	**COVID-19 Associated Multisystem Inflammatory Syndrome in Children (MIS-C).** Individual meets **ALL** of the following are met: 1. Less than 21 years of age 2. Medication is being used for the treatment of Multisystem Inflammatory Syndrome in Children (MIS-C) 3. **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 4. 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, 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) 5. Other causes have been excluded

	6. 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 experimental, investigational or unproven.**
Molnupiravir (Lagevrio™)	**COVID-19**. Individual meets **ONE** of the following: **1. ALL** of the following: A. 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) B. 18 years of age or older C. At high risk for progressing to severe COVID-19 D. Alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate (for example, bebtelovimab, Paxlovid) E. Molnupiravir must be in accordance with the authorized Health Care Provider Fact Sheets **2.** Previously received molnupiravir, then **ALL** of the following: A. 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. B. At least 90 days have elapsed since completion of the initial course of molnupiravir for treatment of COVID-19 C. Alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate (for example, Paxlovid) *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)* • *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* **Authorization is for one course of treatment (40 capsules) for a duration of 5 days.** **Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):** 1. **Less than 18 years of age** 2. **Initiation of treatment in individual 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. 3. **Pre-Exposure or Post-Exposure Prophylaxis for prevention of COVID-19** 4. **For use longer than 5 consecutive days**
Nirmatrelvir and Ritonavir (Paxlovid)	**COVID-19**. Individual meets **ONE** of the following: **1. ALL** of the following are met: A. Diagnosis 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. 12 years of age and older, weighing at least 40 kg C. At high risk for progressing to severe COVID-19 D. Use of Paxlovid covered by this authorization must be in accordance with the authorized Fact Sheets **Authorization is for one course of treatment (1 carton of 5 blister cards) every 120 days** **2.** <u>Previously received Paxlovid</u>, then **ALL** of the following: A. 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. B. At least 90 days have elapsed since completion of the initial course of Paxlovid for treatment of COVID-19 <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* **Authorization is for one course of treatment (30 tablets/1 carton of 5 blister cards) for a duration of 5 days.** **Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):** 1. **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. 2. **Pre-Exposure or Post-Exposure Prophylaxis for prevention of COVID-19** 3. **For use for longer than 5 consecutive days**
Remdesivir (Veklury®)	**COVID-19, Treatment.** Individual meets **ONE** of the following: 1. <u>If Hospitalized</u>**, BOTH** of the following: A. Used for the treatment of coronavirus disease 2019 (COVID-19) infection B. Administered via intravenous (IV) infusion 2. <u>If Non-Hospitalized</u>, **ALL** of the following: A. Weighs 3.5 kg or greater (approximately 7-8 lbs) B. Mild to moderate COVID-19 who are at high risk of disease progression C. Administered via intravenous (IV) infusion within 7 days of symptom onset <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* **Dosing. ONE** of the following regimens: 1. If at least 40 kg (approximately 88 lbs), **BOTH** of the following: A. Loading dose: 200 mg intravenous (IV) given once on Day 1 of therapy B. Maintenance dose: 100 mg IV given once daily beginning on Day 2 2. If at least 3 kg and less than 40 kg (approx. 6.6 lbs to 88 lbs), **BOTH** of the following: A. Loading dose: 5 mg/kg IV given on Day 1 B. Maintenance dose: 2.5 mg/kg IV given once daily beginning on Day 2 **Authorization Duration:** • For Hospitalized, duration of therapy is up to 10 days. • For Outpatient treatment, duration of therapy is up to 3 days. **Any other use is considered experimental, investigational or unproven.**
Sarilumab (Kevzara)	**COVID-19 - Hospitalized.** Individual meets **ALL** of the following: A. 2 years of age to 17 years of age B. Hospitalized with a diagnosis of COVID-19 C. Receiving systemic corticosteroids D. Requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO E. Documented inability to obtain tocilizumab intravenous **Any other use in the management of COVID-19 is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):** **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.[3,4]
Tocilizumab intravenous (Actemra IV®)	**ONE** of the following: **1. COVID-19 - Hospitalized**. Individual meets **ALL** of the following: A. 2 years of age or older B. Hospitalized with a diagnosis of COVID-19 C. Receiving systemic corticosteroids D. Requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO E. Actemra will be administered only via intravenous infusion **2. COVID-19 Associated Cytokine Release Syndrome (CRS)**. Diagnosis of Cytokine Release Syndrome (CRS) associated with COVID-19.

	Any other use in the management of COVID-19 is considered experimental, investigational or unproven, including the following (this list may not be all inclusive): **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.[3,4]
Tofacitinib **(Xeljanz/ Xeljanz XR)**	**COVID-19 - Hospitalized.** Individual meets **ALL** of the following: 1. 2 years of age or older 2. Treatment of suspected, or laboratory confirmed, COVID-19 3. Is hospitalized requiring supplemental oxygen, invasive mechanical ventilation, or ECMO 4. Documented inability to obtain baricitinib 5. Use is for a maximum of 14 days or until discharge from the hospital, whichever comes first *Tofacitinib may be administered with or without remdesivir.* **Any other use in the management of COVID-19 is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):** **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.[3,4]

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.

Coding Information

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
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 supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) only, includes infusion and post administration monitoring, second dose
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

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 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 04/05/2022]
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-Approved Indication

Drug	FDA-approved Indication
Remdesivir (Veklury®)[37]	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.
Baricitinib (Olumiant)[40]	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).
Tocilizumab (Actemra)[46]	Actemra® (tocilizumab) is indicated for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adult patients who are receiving systemic corticosteroids and require supplemental oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

FDA Prescribing Information

Drug	Prescribing Information

Baricitinib (Olumiant)[40]	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®)[37]	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.
Tocilizumab (Actemra)[46]	**Administer Actemra by intravenous infusion only.** The recommended dosage of Actemra for treatment of adult patients with COVID-19 is 8 mg per kg administered as a single 60-minute intravenous infusion. 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. • Doses exceeding 800 mg per infusion are not recommended in patients with COVID-19 • Subcutaneous administration is not approved for COVID-19

Health Care Provider FDA EUA Fact Sheet

Anakinra (Kineret)[45]	Authorization of Use The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of Kineret 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). In the SAVE-MORE trial used to support the efficacy and safety of KINERET in COVID-19, key exclusion criteria were: pO2/FiO2 ratio < 150 mmHg, requirement for non-invasive ventilation (NIV), requirement for mechanical ventilation (MV), requirement for extra-corporeal membrane oxygenation (ECMO), and < 1500 neutrophils/mm3. All enrolled patients were required to have a plasma soluble urokinase plasminogen activator receptor (suPAR) level ≥ 6 ng/mL [see Clinical Studies (14.1)]. The suPAR assay is not commercially available in the United States. In order to identify a comparable population as was studied in the SAVE-MORE trial, an alternative patient identification method was developed to select patients most likely to have suPAR ≥ 6 ng/mL based on commonly measured patient characteristics. Patients meeting at least three of the following eight criteria are considered likely to have suPAR ≥ 6 ng/mL at baseline:

- Age ≥ 75 years
- Severe pneumonia by WHO criteria
    - WHO criteria is available at: https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov
- Current/previous smoking status
- Sequential Organ Failure Assessment (SOFA) score ≥ 3 5
- Neutrophil-to-lymphocyte ratio (NLR) ≥ 7 6
- Hemoglobin ≤ 10.5 g/dL 7. Medical history of ischemic stroke 8. Blood urea ≥ 50 mg/dL and/or medical history of renal disease

Recommended Dosage for COVID-19

- The recommended dosage of Kineret for the treatment of adults with COVID-19 is 100 mg administered daily by subcutaneous injection for 10 days. Each syringe is intended for a single use. A new syringe must be used for each dose. Any unused portion after each dose should be discarded.
- Renal Impairment: consider administration of Kineret 100 mg every other day by subcutaneous injection for a total of 5 doses over 10 days in patients who have severe renal insufficiency or end stage renal disease (defined as creatinine clearance < 30 mL/min, as estimated from serum creatinine levels)

The SOFA Score

***Organ System,* Measurement**	**SOFA Score**				
	0	1	2	3	4
Respiration PaO_2/FiO_2, mmHg	Normal	<400	<300	<200 (with respiratory support)	<100 (with respiratory support)
Coagulation Platelets $x10^3/mm^3$	Normal	<150	<100	<50	<20
Liver Bilirubin, mg/dL (µmol/l)	Normal	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (<204)
Cardiovascular Hypotension	Normal	MAP<70 mmHg	Dopamine ≤5 or dobutamine (any dose)**	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central Nervous System Glasgow Coma Score	Normal	13-14	10-12	6-9	<6
Renal Creatinine, mg/dL (µmol/l) or Urine output	Normal	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) or <500 mL/day	>5.0 (>440) or <200 mL/day

**Adrenergic agents administered for at least 1 hour (doses given are in mcg/kg/min).

SOFA is available at: https://files.asprtracie.hhs.gov/documents/aspr-tracie-sofa-score-fact-sheet.pdf.

Baricitinib (Olumiant)[11]

AUTHORIZED USE

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.

INSTRUCTIONS FOR ADMINISTRATION

	Pediatric Patients • 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 ○ For patients who are unable to swallow whole tablets, alternate administration may be considered: • Oral dispersion • Gastrostomy tube (G tube) • Nasogastric tube (NG tube)
Gohibic (vilobelimab)	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]	**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™)[15]	**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.
Tocilizumab (Actemra IV)[18]	**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:

	Recommended Intravenous Dosage for COVID-19 Patients less than 30 kg weight: 12 mg/kg Patients at or above 30 kg weight: 8 mg/kg 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.

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 not 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).

Sarilumab (Kevzara)

National Institute of Health (NIH) COVID-19 Treatment Guidelines[4]

- **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) [3]

- **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)**

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.[4]

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.[36]

Tofacitinib (Xeljanz / Xeljanz XR)

National Institute of Health (NIH) COVID-19 Treatment Guidelines[4]

- **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.**
- 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) [3]

- **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)**
- 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.

Guideline Evidence Rating Scales

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

Anakinra (Kineret)

Date	EUA Letter
11/8/2022	On November 8, 2022 the FDA issued an emergency use authorization for anakinra (Kineret) for the treatment of 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 for progressing to severe respiratory failure and are likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR).[43] **Scope of Authorization** • Kineret may only be used by healthcare providers to treat 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 for progressing to severe respiratory failure and are likely to have an elevated suPAR • The use of Kineret covered by this authorization must be in accordance with the authorized Fact Sheets Safety and Efficacy Based on the totality of scientific evidence available to FDA, including data from the clinical trial SAVE-MORE (NCT04680949): a randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Kineret in adult (≥ 18 years) patients with COVID-19 pneumonia who were at risk of developing severe respiratory failure, it is reasonable to believe that Kineret may be effective for the treatment of 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), as described in the Scope of Authorization (Section II), and when used under the conditions described in this authorization, the known and potential benefits of Kineret outweigh the known and potential risks of such product.

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. [11] **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 a 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. [11] 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 supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). [11] 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.

Molnupiravir

Date	EUA Letter
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]

	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.

<u>Product description</u>
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).[14]

<u>Nirmatrelvir and ritonavir (Paxlovid)</u>

Date	EUA Letter
10/27/2022	Re-issued. [41]

8/5/2022	Re-issued. [41]
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. [41] <u>New addition to Scope of Authorization</u> 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. [41] 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 <u>not</u> 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.[41]

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.[32] **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

Vilobelimab (Gohibic)

Date	EUA Letter
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] **Scope of Authorization** • GOHIBIC may only be used by healthcare providers for the treatment of COVID-19 in hospitalized adults when initiated within 48 hours of receiving IMV, or ECMO • The use of GOHIBIC covered by this authorization must be in accordance with the authorized Fact Sheets.

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]

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:* o Hospitalized, or o 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.[19]

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 <u>NOT</u> 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]

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

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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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. 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%	8/31/2021
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:	1/4/2022

Summary of Changes (1/1/2021 - Present)	Date
• 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	
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 2/23/2022 • 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
Minor **changes** in coverage criteria: • 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
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

Summary of Changes (1/1/2021 - Present)	Date
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: • Modified 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: Override criteria were updated 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