Drug Monograph

Drug Name: **REGN-COV2 (casirivimab/imdevimab) vials**
Drug Class: **COVID-19 Monoclonal Antibodies**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Casirivimab is available in 300 mg/2.5 ml and 1332 mg in 11.1 ml vials. Imdevimab is available in 300 mg/2.5 ml and 1332 mg in 11.1 ml vials.
Manufacturer:	Manufactured by: Regeneron Pharmaceuticals, Inc. Tarrytown, NY 10591.
Summary of Findings:	The efficacy of REGN-COV2 was investigated in a randomized, double-blind, placebo controlled Phase 2/3 trial of 799 non-hospitalized patients with documented SARS-CoV-2 infection. Patients were randomized to receive REGN-COV2 2,400 mg, 8,000mg or placebo. The primary endpoint in Phase 2 was the average daily change in viral load through Day 7. The primary endpoint analysis showed a greater than tenfold reduction in viral load versus placebo. The primary endpoint in Phase 3, cohort 1 evaluated the clinical efficacy of REGN-CoV2 comparing the COVID-19-related medically-attended visits among the treatment group versus placebo. Medical visits were reduced by 57% through Day 29 (2.8% vs. 6.5%; p=0.024). Medical visits in patients with one or more risk factors were reduced by 72%.

Status Recommendation:	☐ Clinical Edit ☒ Open Access	☐ PA Required ☐ PDL
Type of PA Criteria:	☐ Appropriate Indications ☒ No PA Required	☐ Non-Preferred ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus, SARS-CoV-2. The virus spreads primarily through droplets of saliva or discharge from the nose when an infected person coughs or sneezes. The most common way to confirm infection from the virus is using a Polymerase Chain Reaction (PCR) test after collecting samples from the nose and/or throat. The most common symptoms of COVID-19 are fever, dry cough and fatigue. Other symptoms include loss of taste or smell, nasal congestion, conjunctivitis, sore throat, headache, muscle or joint pain, different types of skin rash, nausea or vomiting, diarrhea, chills or dizziness. Severe symptoms of COVID-19 include shortness of breath, loss of appetite, confusion, persistent pain or pressure in the chest, and high temperature. Other less common symptoms are irritability, reduced consciousness (sometimes associated with seizures), anxiety, depression, sleep disorders, more severe and rare neurological complications such as strokes, brain inflammation, delirium, and nerve damage. People aged 60 years and older, and those with underlying medical problems like hypertension, cardiovascular disease, diabetes, obesity, or cancer are at higher risk of developing serious illness. Some people continue to experience symptoms past the 10 to 14 days expected with viral infections and there are groups working to determine what long-term effects COVID-19 may have on patients experiencing any level of severity of the disease. Current treatments for the illness includes supportive care for the hospitalized patient such as supplemental oxygen and more advanced respiratory support (i.e., ventilation) and dexamethasone. The WHO's Solidarity Trial indicated that remdesivir, hydroxychloroquine, lopinavir/ritonavir and interferon regimens appear to have little or no effect on 28-day mortality or the in-hospital course of COVID-19 among hospitalized patients. The WHO does not recommend self-medication with any medicines, including antibiotics, at home as a prevention or cure for COVID-19. Vaccines from Pfizer and Moderna have been granted Emergency Use Authorization (EUA) by the Food and Drug Administration (FDA) and distribution across the country and administration to those at highest risk has begun.

Dosage Form [3]

Casirivimab is available in 300 mg/2.5 ml and 1332 mg in 11.1 ml vials. Imdevimab is available in 300 mg/2.5 ml and 1332 mg in 11.1 ml vials.

Manufacturer [4]

Manufactured by: Regeneron Pharmaceuticals, Inc., Tarrytown, NY 10591.

Indication(s) [4]

Emergency use authorization (EUA): For the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection resulting in mild to moderate coronavirus disease 2019

(COVID-19) in adults and pediatric patients (≥12 years of age and ≥40 kg) who are at high risk for progressing to severe COVID-19 or requiring hospitalization.
High risk is defined as patients who meet at least one of the following criteria:

- Have a body mass index (BMI) ≥35
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥65 years of age
- Are ≥55 years of age AND have:
  - Cardiovascular disease, OR
  - Hypertension, OR
  - Chronic obstructive pulmonary disease/other chronic respiratory disease

Are 12-17 years of age AND have

- BMI ≥85th percentile for their age and gender based on CDC growth charts, OR
- Sickle Cell disease, OR
- Congenital or acquired heart disease, OR
- Neurodevelopmental disorders (i.e., cerebral palsy), OR
- A medical-related technological dependence (i.e., tracheostomy, gastrostomy, or positive pressure ventilation not related to COVID-19), OR
- Asthma, reactive airway or other chronic respiratory disease that requires daily medication for control

Limitations of authorized use: Casirivimab and imdevimab are not authorized for use in patients:

- Who are hospitalized due to COVID-19, OR
- Who require oxygen therapy due to COVID-19, OR
- Who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity

Clinical Efficacy [3,4,5,6] (mechanism of action/pharmacology, comparative efficacy)

Casirivimab and imdevimab are recombinant human immunoglobulin G-1 (IgG1) monoclonal antibodies used in combination as an antiviral medication to target severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The antibodies bind to non-overlapping epitopes of the spike protein receptor binding domain (RBD) of SARS-CoV-2, which prevents the virus from interacting with the human ACE2 receptor. In Jurkat target cells expressing SARS-CoV-2 spike proteins, the combination of casirivimab plus imdevimab elicited antibody-dependent cell-mediated cytotoxicity (ADCC) with human natural killer (NK) effector cells and antibody-dependent cellular phagocytosis (ADCP) with human macrophages. However, the combination did not mediate complement-dependent cytotoxicity in cell-based assays.

Pharmacokinetics:

Absorption	NA
Metabolism	NA
Excretion	NA
Half-life	NA

Clinical Trials Experience:

STUDY DESIGN (NCT 04425629)	Phase 2/3, randomized, double-blind, placebo-controlled trial (n=799)

INCLUSION CRITERIA	• Has SARS-CoV-2-positive antigen or molecular diagnostic test ≤72 hours prior to randomization • Cohort 1: Has symptoms consistent with COVID-19 with onset ≤7 days before randomization • Cohort 2: Has symptoms consistent with COVID-19 with onset ≤7 days before randomization, or is asymptomatic at randomization and has no prior symptoms consistent with COVID-19 • Maintains O_2 saturation ≥93% on room air • Is able to understand and complete study-related questionnaires
EXCLUSION CRITERIA	• Was admitted to a hospital for COVID-19 prior to randomization, or is hospitalized (inpatient) for any reason • Has participated, or is participating, in a clinical research study evaluating COVID-19 convalescent plasma, mAbs against SARS-CoV-2, or IVIG within 3 months or within 5 half-lives of the investigational product (whichever is longer) prior to the screening visit • Prior, current, or planned future use of any of the following treatments: COVID-19 convalescent plasma, mAbs against SARS-CoV-2, IVIG (any indication), systemic corticosteroids (any indication), or COVID-19 treatments (authorized, approved, or investigational)
TREATMENT REGIMEN	Patients were randomized to receive 2,400 mg, 8,000 mg or placebo.
INTERIM RESULTS	The primary endpoint in Phase 2 was the average daily change in viral load through Day 7. The primary endpoint analysis showed a greater than tenfold reduction in viral load versus placebo (-0.56 $\log_{10}$ copies/ml [95% CI: -1.02, -0.11] vs. -0.41 $\log_{10}$ copies/ml [95% CI: -0.71, -0.10]). Patients with higher viral load at baseline and/or no detectable antibodies at baseline derived greater benefit from REGN-COV2 therapy. The primary endpoint in Phase 3, cohort 1 evaluated the clinical efficacy of REGN-CoV2 comparing the COVID-19-related medically-attended visits among the treatment group versus placebo. Medical visits were reduced by 57% through Day 29 (2.8% vs. 6.5%; p=0.024). Medical visits in patients with one or more risk factors (including age >50 years, BMI >30, cardiovascular, metabolic, lung, liver or kidney disease; or immunocompromised status) were reduced by 72%.
SAFETY	Discussed in the Adverse Effects section below.

Contraindications [(4)]

- None

Warnings and Precautions [(4)]

- This EUA is for the use of unapproved products for specific patients and with limitations

for use under the EUA.

- Casirivimab and imdevimab must be administered together after dilution by IV infusion only in settings in which health care providers have immediate access to medication to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.
- Health care providers must submit a report on all medication errors and all serious adverse events potentially related to casirivimab and imdevimab.

Adverse Effects [4]

Most common	2,400 mg treatment group (N=258)	8,000 mg treatment group (N=260)	Placebo (N=262)
Pneumonia	√		√
Hyperglycemia	√		
Nausea and vomiting	√		√
Intestinal obstruction		√	
Dyspnea		√	
COVID-19			√
Hypoxia			√
Infusion-related reactions		√	

Drug Interactions [4]

- None

Dosage and Administration [5]

The authorized dosage is 1,200 mg of casirivimab and 1,200 mg of imdevimab administered together as a single IV infusion as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset. Stock solutions must be diluted prior to administration. Infusion time must be at least 60 minutes. The patient must be clinically monitored for at least 1 hour after the infusion is complete.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/Dose
Casirivimab and imdevimab	REGN-COV2	Regeneron Pharmaceuticals	2,400 mg IV once	$1500 if not from National Stockpile
Bamlanivimab	LY-CoV555	Eli Lilly	700 mg IV once	$1,250 if not from National Stockpile
Remdesivir	Veklury	Gilead Sciences, Inc	200 mg IV on Day1, then 100 mg daily for 5 to 10 days	$520 per 100 mg if not from National Stockpile

** Wholesale Acquisition Cost

Conclusion

REGN-COV2 has been granted EUA by the FDA for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection resulting in mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (≥12 years of age and ≥40 kg) who are at high risk for progressing to severe COVID-19 or requiring hospitalization. The antibodies bind to non-overlapping epitopes of the spike protein receptor binding domain (RBD) of SARS-CoV-2, which prevents the virus from interacting with the human ACE2 receptor. In Jurkat target cells expressing SARS-CoV-2 spike proteins, the combination of casirivimab plus imdevimab elicited antibody-dependent cell-mediated cytotoxicity (ADCC) with human natural killer (NK) effector cells and antibody-dependent cellular phagocytosis (ADCP) with human macrophages. The efficacy of REGN-COV2 was investigated in a randomized, double-blind, placebo controlled Phase 2/3 trial of 799 non-hospitalized patients with documented SARS-CoV-2 infection. Treatment with REGN-COV2 showed a tenfold reduction in viral load at Day7 compared to placebo and reduced medically-related office visits by 57% by Day 29. In those with at least one risk factor, medical visits were reduced by 72%. The most common adverse events were pneumonia, hyperglycemia, nausea and vomiting, intestinal obstruction, dyspnea, COVID-19, hypoxia, and infusion-related reactions.

Recommendation

MO HealthNet Division recommends Open Access status for this product.

References

1) Coronavirus Disease (COVID-19). World Health Organization. https://www.who.int/news-room/q-a-detail/coronavirus-disease-covid-19. November 10, 2020.
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4) Casirivimab and Imdevimab Prescribing Information. https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=f5bf7a31-7e17-4a94-805c-d231ea458fb0&version=4##. December 2020.
5) Casirivimab;Imdevimab. Clinical Pharmacology. https://www.clinicalkey.com/pharmacology/monograph/5289. Accessed December 28, 2020.
6) U.S. National Library of Medicine. Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Adult and Pediatric Patients with COVID-19. https://clinicaltrials.gov/ct2/show/NCT04425629. Accessed December 28, 2020.

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