Preemptive policy: This is a P&T approved policy and can be used until it is superseded by an updated policy.

CENTENE Corporation

Clinical Policy: Casirivimab and Imdevimab (REGEN-COV)

Reference Number: CP.PHAR.520
Effective Date: 12.22.20
Last Review Date: 05.22
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Casirivimab and imdevimab (REGEN-COV) are recombinant human IgG1 monoclonal antibodies that target the receptor binding domain of the spike protein of SARS-CoV-2.

EUA Approved Indication(s)

REGEN-COV, as a co-formulated product or as individual vials administered together, is authorized for emergency use for:

- The treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (≥ 12 years of age and weighing ≥ 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.
  Limitation(s) of authorized use:
  - REGEN-COV is not authorized for treatment of mild to moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency.
    - FDA's determination and any updates are available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatoryand-policy-framework/emergency-use-authorization#coviddrugs.
  - REGEN-COV is not authorized for use in patients:
    - who are hospitalized due to COVID-19, or
    - who require oxygen therapy due to COVID-19, or
    - who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity.
  - Monoclonal antibodies, such as REGEN-COV, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.
- Post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:
  - not fully vaccinated **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications) **and**

- have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC) **or**
- who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons).

Limitation(s) of authorized use:

- REGEN-COV is not authorized for post-exposure prophylaxis of COVID-19 in geographic regions where exposure is likely to have been to a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency.
  - FDA's determination and any updates are available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatoryand-policy-framework/emergency-use-authorization#coviddrugs.
- Post-exposure prophylaxis with REGEN-COV is not a substitute for vaccination against COVID-19.
- REGEN-COV is not authorized for pre-exposure prophylaxis for prevention of COVID-19.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that REGEN-COV is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria*

**Criteria will mirror the clinical information from the prescribing information once FDA-approved*

A. Treatment of COVID-19 (must meet all)**:**

1. Diagnosis of COVID-19 infection via a positive viral test for SARS-CoV-2 within the last 3 days;
2. Member has one or more mild to moderate COVID-19 symptoms;
3. Member is within 10 days of symptom onset;
4. Age ≥ 12 years;
5. Member's body weight is ≥ 40 kg;
6. Member meets at least one of the criteria for being at high risk for progression to severe COVID-19 and/or hospitalization (*see Appendix E*);
7. At the time of request, member meets all of the following (a, b, c, and d):
   a. Infection is not likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency (FDA's determination and any updates are available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs);
   b. Member is not hospitalized due to COVID-19;
   c. Member does not require oxygen therapy due to COVID-19;

d. For members on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity: Member does not require an increase in baseline oxygen flow rate due to COVID-19;

8. Casirivimab and imdevimab will be administered together as a single intravenous infusion;
9. Casirivimab and imdevimab will be administered to the member in a setting in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system, as necessary;
10. Dose does not exceed casirivimab 600 mg and imdevimab 600 mg, one time.

Approval duration: One time

B. Post-exposure Prophylaxis of COVID-19 (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Member is not fully vaccinated;
   b. Member is not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (e.g., individuals with immunocompromising conditions including those taking immunosuppressive medications);
2. Member meets one of the following (a or b):
   a. Member has been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per CDC (*see Appendix F*);
   b. Member is at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (e.g., nursing homes, prisons);
3. Age ≥ 12 years;
4. Member's body weight is ≥ 40 kg;
5. Member meets at least one of the criteria for being at high risk for progression to severe COVID-19 and/or hospitalization (*see Appendix E*);
6. REGEN-COV is not being used for pre-exposure prophylaxis for prevention of COVID-19;
7. At the time of request, member meets all of the following (a, b, c, and d):
   a. Exposure is not likely to have been to a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency (FDA's determination and any updates are available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs);
   b. Member is not hospitalized due to COVID-19;
   c. Member does not require oxygen therapy due to COVID-19;
   d. For members on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity: Member does not require an increase in baseline oxygen flow rate due to COVID-19;
8. Casirivimab and imdevimab will be administered together as a single intravenous infusion;
9. Casirivimab and imdevimab will be administered to the member in a setting in which health care providers have immediate access to medications to treat a severe infusion

reaction, such as anaphylaxis, and the ability to activate the emergency medical system, as necessary;
10. Dose does not exceed casirivimab 600 mg and imdevimab 600 mg for the initial infusion, followed by no more than casirivimab 300 mg and imdevimab 300 mg repeat dosing every 4 weeks.

Approval duration: 3 months

C. Other diagnoses/indications
1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy*

**Criteria will mirror the clinical information from the prescribing information once FDA-approved*

A. Treatment of COVID-19
1. Re-authorization is not permitted.

Approval duration: Not applicable

B. Post-exposure Prophylaxis of COVID-19 (must meet all)**:**
1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member will have ongoing exposure to SARS-COV-2 and is not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination;
3. Dose does not exceed casirivimab 300 mg and imdevimab 300 mg every 4 weeks.

Approval duration: 3 months

C. Other diagnoses/indications
1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

BMI: body mass index
CDC: Centers for Disease Control and Prevention
COVID-19: coronavirus disease 2019
EUA: Emergency Use Authorization
FDA: Food and Drug Administration

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: Contraindications/Boxed Warnings [Pending]
- Contraindication(s): pending
- Boxed warning(s): pending

Appendix D: General Information
- The data supporting the EUA for casirivimab and imdevimab are based on the analysis of Phase 1/2 from trial R10933-10987-COV-2067 (NCT04425629), that occurred after 799 enrolled subjects had completed at least 28 days of study duration. NCT04425629 is a randomized, double-blinded, placebo-controlled clinical trial studying casirivimab and imdevimab for the treatment of adult subjects with mild to moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). The trial enrolled adult subjects who were not hospitalized and had at least 1 or more COVID-19 symptoms that were at least mild in severity. Treatment was initiated within 3 days of obtaining a positive SARS-CoV-2 viral infection determination. Subjects were randomized in a 1:1:1 manner to receive a single intravenous (IV) infusion of 2,400 mg of casirivimab and imdevimab (1,200 mg of each) (n = 266), or 8,000 mg of casirivimab and imdevimab (4,000 mg of each) (n = 267), or placebo (n=266).
- The pre-specified primary endpoint in Phase 1/2 of trial NCT04425629 was the time weighted average (TWA) change from baseline in viral load (log_{10} copies/mL), as measured by RT-qPCR in nasopharyngeal swab samples, in subjects with a positive baseline RT-qPCR value, i.e., the modified full analysis set (mFAS). In the mFAS for the Phase 1/2 analysis, the difference in TWA from Day 1 through Day 7 for the pooled doses of casirivimab and imdevimab compared with placebo (n = 665) was -0.36 log_{10} copies/mL ($p < 0.0001$). The largest reductions in viral load relative to placebo occurred in patients with high viral load (-0.78 log_{10} copies/mL) or who were seronegative (-0.69 log_{10} copies/mL) at baseline. Reductions occurring from Day 1 through Day 11 were similar to those for Day 1 through Day 7.
- While viral load was used to define the primary endpoint in the Phase 1/2 analysis, clinical evidence demonstrating that casirivimab and imdevimab may be effective came from the predefined secondary endpoint, medically attended visits (MAV) related to COVID-19. Medically attended visits comprised hospitalizations, emergency room visits, urgent care visits, or physician office/telemedicine visits for COVID-19. A lower proportion of subjects treated with casirivimab and imdevimab had COVID-19 related MAVs (2.8% for combined treatment arms vs 6.5% placebo). In post-hoc analyses, a lower proportion of subjects treated with casirivimab and imdevimab had COVID-19-related hospitalizations or emergency room visits compared to placebo. Results for this endpoint were suggestive of a relatively flat dose-response relationship. The absolute risk reduction for casirivimab and imdevimab compared to placebo was greater in subjects at high risk for progression to severe COVID-19 and/or hospitalization.
- The median time to symptom improvement, as recorded in a trial-specific daily symptom diary, was 5 days for casirivimab and imdevimab-treated subjects, as compared with 6 days for placebo-treated subjects.

- Per the casirivimab and imdevimab EUA, casirivimab and imdevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system, as necessary.
- There is a potential for serious hypersensitivity reaction, including anaphylaxis, with administration of casirivimab and imdevimab.
- Infusion-related reactions have been observed with administration of casirivimab and imdevimab. Signs and symptoms of infusion-related reactions may include: fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, dizziness.

Appendix E: Criteria for Identifying High Risk Individuals

- The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing ≥ 40 kg) at higher risk for progression to severe COVID-19:
  - Older age (for example, age ≥ 65 years of age)
  - Obesity or being overweight (for example, BMI > 25 kg/m^2, or if age 12-17, 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 REGEN-COV under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medicalconditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

Appendix F: CDC Close Contact Criteria

Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils,

or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Treatment of COVID-19 infection	**IV infusion is strongly recommended. SC injection is an alternative route of administration when intravenous infusion is not feasible and would lead to delay in treatment.** 1,200 mg (600 mg casirivimab with 600 mg imdevimab) IV or SC one time as a single infusion	1,200 mg one time
Post-exposure prophylaxis of COVID-19 infection	**Either SC injection or IV infusion can be used.** Initial dose: 1,200 mg (600 mg casirivimab with 600 mg imdevimab) IV or SC one time as a single infusion Repeat dosing if needed: 600 mg (300 mg casirivimab with 300 mg imdevimab) IV or SC every 4 weeks for the duration of ongoing exposure	Initial dose: 1,200 mg Repeat doses: 600 mg

VI. Product Availability

- Single, co-formulated vial: casirivimab/imdevimab 600 mg/600 mg per 10 mL
- Individual antibody solutions in separate vials: casirivimab 1,332 mg/11.1 mL or 300 mg/2.5 mL vials and imdevimab 1,332 mg/11.1 mL or 300 mg/2.5 mL vials

VII. References

1. Casirivimab and imdevimab EUA re-issued letter of authorization. January 2022. Available at: https://www.fda.gov/media/145610/download. Accessed February 13, 2022.
2. Fact sheet for health care providers Emergency Use Authorization (EUA) of casirivimab and imdevimab. Available at: https://www.regeneron.com/sites/default/files/treatment-covid19-eua-fact-sheet-for-hcp.pdf. Accessed February 13, 2022.
3. Frequently Asked Questions on the EUA for casirivimab and imdevimab. Available at: https://www.regeneroneua.com/faq. Accessed February 13, 2022.
4. ClinicalTrials.gov. Safety, tolerability, and efficacy of anti-spike (S) SARS-CoV-2 monoclonal antibodies for the treatment of ambulatory adult patients with COVID-19. Available at: https://clinicaltrials.gov/ct2/show/NCT04425629?term=R10933-10987-COV-2067&draw=2&rank=1. Accessed December 4, 2020.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-

date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
Q0244	Injection, casirivimab and imdevimab, 1,200 mg
M0243	Intravenous infusion or subcutaneous injection, casirivimab and imdevimab includes infusion or injection, and post administration monitoring
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

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Clinical policy created pre-emptively	12.04.20	12.20
4Q 2021 annual review: updated policy to reflect recent developments on the EUA including: authorization for post-exposure prophylaxis, inclusion of "death" in the definition of "severe" COVID-19, inclusion of a SC dosing option, new co-formulated vial formulation; revised HIM.PHAR.21 to HIM.PA.154; references reviewed and updated.	08.16.21	11.21
2Q 2022 annual review: for post-exposure prophylaxis, added a requirement for documentation that the member is at high risk for disease progression and that the member does not have any limitations against use, per the EUA label; RT4: criteria added to reflect new FDA limitation of use against use in regions where infection or exposure is likely due to a non-susceptible SARS-CoV-2 variant; references reviewed and updated.	02.13.22	05.22

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage

decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.