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Robert Knodell
Acting Director

Michael L. Parson
Governor

August 24, 2021

Standing Order for REGEN-COV (casirivimab and imdevimab) Administration

The Director of the Department of Health and Senior Services, finding it necessary to protect public health and prevent the further spread of COVID-19, pursuant to the authority granted under section 192.020, RSMo, and 19 CSR 20-20.040, hereby orders the following:

Purpose

This Standing Order authorizes eligible healthcare providers who are trained in the administration of REGEN-COV (casirivimab and imdevimab) to administer REGEN-COV:
(1) for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death; and
(2) for post-exposure prophylaxis of COVID-19 in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death,
This Standing Order is in accordance with the Food and Drug Administration's (FDA) Emergency Use Authorization (EUA) for REGEN-COV (casirivimab and imdevimab), as updated (https://www.fda.gov/media/145611/download; https://www.fda.gov/media/145610/download)

Patient Eligibility

Adults and adolescents 12 years of age and older weighing at least 40 kg with positive results of direct SARS-CoV-2 testing within 10 days of symptom onset who meet any of the criteria below.

- Older age (for example, age ≥65 years of age)
- Obesity or being overweight (for example, BMI >25 kg/m2, or if age 12-17, have BMI ≥85th percentile for their age and gender)
- 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, 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 (such as race and ethnicity) that may place individuals at an increased risk for progression to more severe disease. Authorization of REGEN-COV under the current EUA is not limited to the medical conditions or factors listed above.

<u>Monoclonal antibodies are not authorized for use in patients:</u>

- 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.

Procedure

1. Verify that the individual meets the FDA EUA criteria for administration of REGEN-COV (casirivimab and imdevimab)
2. Review and follow the "Intravenous Infusion Preparation and Administration Instructions" and the "Subcutaneous Injection Preparation and Administration Instructions" for qualifying patients receiving infusion (**Attachment A)**
3. Receive informed written consent for use of REGEN-COV (casirivimab and imdevimab) for treatment of COVID-19 or post-exposure prophylaxis from the patient, or parent or legal guardian if the patient is under 18 years of age or incapable of consenting.
4. Submit a report on all medication errors and all serious adverse events potentially related to

REGEN-COV (casirivimab and imdevimab).

5. Advise all patients, or parents or legal guardians if the patient is under 18 years of age or incapable of consenting, to continue to self-isolate and use infection control measures.

6. Provide patient a copy of the Patient Fact Sheet:

• English: treatment-covid19-eua-fact-sheet-for-patient.pdf (regeneron.com)

• Spanish: treatment-covid19-eua-fact-sheet-patient-spanish.pdf (regeneron.com)

Duration of Standing Order

This Standing Order shall remain in effect for the duration of the FDA's EUA for treatment of COVID-19 and post-exposure prophylactic use of REGEN-COV (casirivimab and imdevimab), and the duration of the PREP Act immunity provisions as established in the Declaration as effective on February 4, 2020 and all subsequent Declarations. This Standing Order shall automatically be rescinded upon the revocation of the FDA's EUA for treatment of COVID-19 and post-exposure prophylactic use of REGEN-COV (casirivimab and imdevimab), or the expiration of the COVID-19 immunity protections for covered countermeasures under the PREP Act, whichever occurs first.

Robert Knodell
Acting Director

George Turabelidze, MD

State of Missouri

REGEN-COV™

Procedure and Protocol

Missouri Department of Health and Senior Services

August 24, 2021

Standing Order
Attachment A

2021

Patient Selection and Post-Exposure Prophylaxis

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, for the treatment of mild to moderate coronavirus disease 2019 (COVID -19) in adult 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.

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 at least 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.
Health care providers should consider the benefit-risk for an individual patient.

Post-Exposure Prophylaxis

This protocol is for the use of REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID -19, including hospitalization or death, and are:

• not fully vaccinated or who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications) and

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

- who are at high risk of exposure to an individual infected with SARS-CoV2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) [see Limitations of Authorized Use].

Limitations of Authorized Use

- REGEN-COV (casirivimab and imdevimab) is not authorized for use in patients:
  - who are hospitalized due to COVID-19, OR
  - who require oxygen therapy due to COVID-19, OR
  - who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 relatedcomorbidity.

- 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.

Available Dosage Forms of REGEN-COV:

REGEN-COV (casirivimab and imdevimab) is available as:

1. A single vial which contains two antibodies co-formulated in a 1:1 ratio of casirivimab and imdevimab

2. Individual antibody solutions in separate vials, which may be supplied in separate cartons or in a dose pack. The dose pack contains individual vials of casirivimab and imdevimab, configurations that may vary in vial size, strength and appearance and are available in configurations that include 2 and 8 cartons (see below)

NDC 61755-**035**-02
Combination of 2 vials
1 vial of casirivimab 11.1 mL
AND
1 vial of imdevimab 11.1 mL

NDC 61755-**036**-08
Combination of 8 vials
4 vials of casirivimab 2.5 mL
AND
4 vials of imdevimab 2.5 mL

Storage and Handling

Casirivimab and Imdevimab are preservative-free. Discard any unused portion.

Store unopened vials in a refrigerator at 2 ºC to 8 ºC (36 ºF to 46 ºF) in the original carton to protect from light.

DO NOT FREEZE.
DO NOT SHAKE.
DO NOT EXPOSE TO DIRECT LIGHT OR HEAT.

If given by intravenous infusion, solution in vial requires dilution prior to administration. The prepared infusion solution is intended to be used immediately. If immediate administration is not possible, store diluted casirivimab and imdevimab solution in the refrigerator at 2 ºC to 8 ºC (36 ºF to 46 ºF) for no more than 36 hours or at room temperature up to 25 °C (77 °F) for no more than 4 hours. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.

If given by subcutaneous injections, the prepared syringes should be administered immediately. If immediate administration is not possible, store the prepared casirivimab and imdevimab syringes in the refrigerator between 2 ºC to 8 ºC (36 ºF to 46 ºF) for no more than 4 hours or at room temperature up to 25 ºC (77 ºF) for no more than 4 total hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 20 minutes prior to administration.

Basic Equipment

Equipment requirements may vary by medical direction. Follow your local requirements when determining the equipment needed for your treatment setting. The following equipment should be considered to ensure the most optimal care environment for patients receiving REGEN-COV. This list is not intended to substitute for your independent medical judgment.

PPE
Gloves
Gowns
Eye and face protection (e.g., goggles, safety glasses, face shields)
NIOSH-certified facepiece respirators or better

Infusion Supplies
Administration set
- Sterile in-line 0.2/0.22 micron filter (may be integrated into administration set or separate add-on device)

IV and catheters
Infusion pumps (if available)
3-mL saline syringes
Appropriately sized syringes
Alcohol wipes
2x2 gauze pads
Adhesive bandages
Occlusive dressing
Absorbent underpads (blue pads)
Extension set tubing
18- gauge stainless steel needles
Sharps Container
Tape

Injection Supplies
3-mL or 5-mL polypropylene Luer lock with Luer connection
21- gauge 1.5-inch transfer needles
25-gauge or 27-gauge needle for subcutaneous injection

General Supplies
Infusion reaction kit
Vital signs equipment
Reaction management kit
- IV diphenhydramine, IV corticosteroid (e.g., methylprednisolone 125 mg), epinephrine (auto-injector preferred), oxygen and delivery devices (nasal cannula and non-rebreather mask)

Locking refrigerator with temperature monitoring capability
Biohazard disposal bag
Disposable disinfecting wipes
Thermometer probe covers (if required)
70% alcohol wipes
Paper towels
Trash bins and liners

Intravenous Infusion Preparation and Administration Instructions

1. Remove the casirivimab and imdevimab vial(s) from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. Do not expose to direct heat. Do not shake the vial(s).

2. Inspect casirivimab and imdevimab vials visually for particulate matter and discoloration prior to administration. Should either be observed, the vial must be discarded and replaced with a new vial.
   - The solution for each vial should be clear to slightly opalescent, colorless to pale yellow

3. Obtain a prefilled intravenous infusion bag containing either 50 ml, 100 ml, 150 ml, or 250 mL of 0.9% Sodium Chloride Injection.

4. Withdraw the appropriate amount of casirivimab and imdevimab from the vial(s) and inject into a prefilled infusion bag containing 0.9% Sodium Chloride Injection.

Size of prefilled 0.9% Sodium Chloride infusion bag	Preparing using co-formulated casirivimab and imdevimab vial	Preparing casirivimab and imdevimab using individual vials[a] Individual vials may be supplied in dose packs
50 mL	Add 10 mL of co-formulated casirivimab and imdevimab (one vial) into a prefilled 0.9% Sodium Chloride infusion bag and administer as instructed on the following page	**ADD:** • 5 mL of casirivimab. May use: ◦ Two vials of 2.5 mL **OR** ◦ One vial of 11.1 mL **AND** • 5 mL of imdevimab. May use: ◦ Two vials of 2.5 mL **OR** ◦ One vial of 11.1 mL and inject into a prefilled 0.9% Sodium Chloride infusion bag and administer as instructed on the following page
100 mL		
150 mL		
250 mL		

5. Gather the recommended materials for infusion:
   a. Polyvinyl chloride (PVC), polyethylene (PE)-lined PVC, or polyurethane (PU) infusion set containing a 0.20 micron in-line polyethersulfone (PES) filter.

6. Attach the infusion set to the IV bag and prime.
   a. Administer the infusion solution via pump or dial-a-flow per chart below
   b. Prepared infusion is not to be administered with any other drug as compatibility is unknown

Size of prefilled 0.9% Sodium Chloride infusion bag used	Maximum infusion rate	Minimum infusion time
50 mL[a]	180 mL/hr	20 minutes
100 mL	310 mL/hr	21 minutes
150 mL	310 mL/hr	31 minutes
250 mL	310 mL/hr	50 minutes

7. Once infusion is complete, flush the infusion line to ensure delivery of the required dose.

8. Clinically monitor patients during administration.
   a. Pre-administration vital signs, then every 10-minutes and at completion of infusion

Gravity Drip Rates

DRIP RATES FOR 10-DROPS/mL ADMINISTRATION SETS

VTBI (mL)	Duration (min)	Rate (mL/hr)	Drops per minute	Drops per 15 seconds
60	20	180	**30**	**8**
110	21	310	**52**	**13**
160	31	310	**52**	**13**
260	50	310	**52**	**13**

DRIP RATES FOR 15-DROPS/mL ADMINISTRATION SETS

VTBI (mL)	Duration (min)	Rate (mL/hr)	Drops per minute	Drops per 15 seconds
60	20	180	**45**	**11**
110	21	310	**78**	**19**
160	31	310	**78**	**19**
260	50	310	**78**	**19**

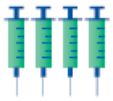
DRIP RATES FOR 20-DROPS/mL ADMINISTRATION SETS

VTBI (mL)	Duration (min)	Rate (mL/hr)	Drops per minute	Drops per 15 seconds
60	20	180	**60**	**15**
110	21	310	**103**	**26**
160	31	310	**103**	**26**
260	50	310	**103**	**26**

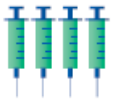
Subcutaneous Injection Preparation and Administration Instructions

Remove the casirivimab and imdevimab vial(s) from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. Do not expose to direct heat. Do not shake the vial(s).

Inspect casirivimab and imdevimab vial(s) visually for particulate matter and discoloration prior to administration. Should either be observed, the vial must be discarded and replaced with a new vial.
The solution for each vial should be clear to slightly opalescent, colorless to pale yellow.



1. 600 mg of casirivimab and 600 mg of imdevimab should be prepared using four syringes. Obtain four 3-mL or 5-mL polypropylene Luer lock syringes with Luer connection and four 21-gauge 1½-inch transfer needles.



2. Withdraw 2.5 mL into each syringe (total of four syringes). Prepare all four syringes at the same time.
   • If individual vials of casirivimab and imdevimab are being used, consider labeling syringes during preparation to ensure the two syringes of casirivimab and two syringes of imdevimab are identifiable

Prepare 600 mg of casirivimab and 600 mg of imdevimab	Preparation of four syringes
Using casirivimab and imdevimab co-formulated vial	• Withdraw 2.5 mL solution per syringe into FOUR separate syringes
Using casirivimab and imdevimab individual vials	**Casirivimab:** Withdraw 2.5 mL solution per syringe into TWO separate syringes. May use: • Two vials of 2.5 mL **OR** • One vial of 11.1 mL (approximately half of the vial) **AND** **Imdevimab:** Withdraw 2.5 mL solution per syringe into TWO separate syringes. May use: • Two vials of 2.5 mL **OR** • One vial of 11.1 mL (approximately half of the vial) For a total of four syringes

3. Replace the 21-gauge transfer needle with a 25-gauge or 27-gauge needle for subcutaneous injection.

4. Administer the subcutaneous injections consecutively, each at a different injection site, into the thigh, back of the upper arm, or abdomen, except for 2 inches (5 cm) around the navel. The waistline should be avoided

- When administering the subcutaneous injections, it is recommended that providers use different quadrants of the abdomen or upper thighs or back of the upper arms to space apart each 2.5-mL subcutaneous injection of casirivimab and imdevimab. DO NOT inject into skin that is tender, damaged, bruised, or scarred

5. Clinically monitor patients after injections and observe patients for at least 1 hour

Adverse Reactions and Reporting

Healthcare providers should direct questions about REGEN-COV (casirivimab with imdevimab) packaging or use to the Regeneron Medical Information Department at 1-844-734-6643 or to medical.information@regeneron.com.

Under the EUA, all serious adverse events and medication errors potentially related to casirivimab and imdevimab must be reported within 7 calendar days from the onset of the event. Serious adverse event reports and medication error reports should be submitted to FDA's MedWatch program using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
- Complete and submit a postage-paid Form FDA 3500 https://www.fda.gov/media/76299/download) and return by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or by fax (1-800-FDA-0178), or
- Call 1-800-FDA-1088 to request a reporting form.

Monitor for adverse reactions (e.g. anaphylaxis) for minimum of one hour and initiate immediate treatment (below) as needed

If mild injection site reaction or allergic reaction consult ordering physician/On-Line Medical Control (OLMC) for management

If signs of severe allergic reaction/anaphylaxis (dyspnea, stridor, severe urticaria, tachycardia, hypotension, or Altered Mental Status) activate emergency response system and initiate treatment if available:

- Epinephrine 0.3 mg (1mg/mL concentration) intramuscular (may use epinephrine auto-injector if available)
- Perform Airway Management as required per local EMS protocols
- Establish IV/IO access and initiate cardiac monitoring
- Diphenhydramine 50 mg IV/IO or intramuscular
- Methylprednisolone sodium succinate 125 mg IV/IO
- Albuterol 2.5 mg nebulized if wheezing/dyspnea, may repeat x 1
- Obtain 12-lead ECG after any epinephrine administration
- Initiate transport per local EMS protocols
- Consult OLMC for additional epinephrine/epinephrine drip as needed