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Considerations for Use of Monoclonal Antibody Therapy for the Treatment of COVID-19 in Congregate Living Settings
September 13, 2021

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These considerations can guide providers with decision making in the use of monoclonal antibody therapy for the treatment of mild to moderate severity COVID-19 illness for persons residing in congregate living settings. These considerations focus on casirivimab and imdevimab (REGEN-COV) as treatment for mild to moderate COVID-19, given *subcutaneously* in skilled nursing facilities (SNFs) and assisted living facilities (ALFs).

Other options for the use of monoclonal antibody therapy include *intravenous* administration for mild to moderate COVID-19 illness and use for post-exposure-prophylaxis. These options are not covered here in detail. Information and the referral process for monoclonal antibody via IV infusion at an infusion site in Minnesota can be accessed using the Minnesota Resource Allocation Platform (MNRAP) at https://www.health.state.mn.us/diseases/coronavirus/mnrap.html

We believe efforts to use this therapy on-site for persons with symptomatic COVID-19 is, at the present time (September 2021), likely to benefit the most people, and is the most feasible, in the majority of SNFs/ALFs in Minnesota. This new process is likely to be most successful, in most facilities, Monday-Friday during daytime hours; at least initially. Providers should also follow guidance from their own provider group or hospital-system. This information changes frequently and this document is current as of the date it was written.

Two Fact Sheets are important to understanding this therapy and are referred to throughout these considerations. These Fact Sheets are updated frequently and must be consulted regularly for the most up-to date information.

1. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of REGEN-COV (casirivimab and imdevimab), found at: https://www.fda.gov/media/145611/download

2. Fact Sheet for Patients, Parents and Caregivers Emergency Use Authorization (EUA) Of REGEN-COV (Casirivimab And Imdevimab) For Coronavirus Disease 2019 (COVID-19), found at: https://www.fda.gov/media/145612/download

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Initial Preparatory Steps	
Facilities	● Identify and train nurses who can receive, draw up, and administer the medication subcutaneously ● Identify on-site medication storage location ● Determine how monitoring will occur and be documented ● Work with pharmacy to determine medication ordering requirements –including whether supplies to draw up and administer the medication will be supplied from the pharmacy or already on-site ● Determine whether anaphylaxis e-kit will come from pharmacy or meds already on site (Epi-Pen, Benadryl)
Medical Directors (SNFs)	● Develop procedures in conjunction with facility leadership, for all the above ● Communicate with your facility's pharmacy to understand their process ● Communicate with providers at your facility so they are familiar with the process and understand the importance of this as the emerging standard of care

Pharmacies	● Order doses from AmerisourceBergen ● Have process for ordering additional supplies and the timeline from ordering to receiving ● Determine process for providers to order medication – collaborate with facility medical director (if SNF) ● Determine whether supplies (syringes, needles) and anaphylaxis e-kit are already onsite or need to be sent out with the medication ● Determine stat delivery process ● Develop messages and materials to communicate with facilities about these processes
Medical Provider	● Understand the use of monoclonal antibody treatment for patients with mild to moderate COVID-19 including how to identify eligible patients, how to order, and the potential for, and type of, adverse reactions

Overview of Administration	
Facilities	● Notify the medical provider about residents with COVID-19 positive tests immediately, **regardless of vaccination status,** and report any symptoms the resident is experiencing. This includes residents discovered positive on surveillance/screening testing, or who tested positive as an evaluation for symptoms. ● Upon receipt of the REGEN-COV from the pharmacy, administer subcutaneously as directed by the pharmacy; syringes may come pre-filled or may be drawn up on-site [see Appendix 1] ● Careful attention to the timeframe for administration of the drug upon receipt from the pharmacy is required ● Supply the resident with the patient fact sheet and/or email to the resident's family ● Monitor by maintaining visual contact for one hour by a person who can summon medical support in case of any adverse reaction symptoms [See Appendix 3]
Medical Directors	● Support medical providers and nursing staff in this new process ● Verify the current patient fact sheets are available
Pharmacies	● Contact facility to alert stat delivery is in process ● Send REGEN-COV and any additional (supplies, anaphylaxis e-kit) if applicable
Medical Provider	● Determine if a patient is eligible for monoclonal antibody therapy and assess for appropriateness of treatment based on COVID-19 illness severity; vaccination status is not a factor in determining whether a patient is eligible to receive monoclonal antibody treatment. Recognize that it is often difficult to discern subtle early symptoms in some patients. ● Convey information to the patient/family (POA) including that the medication is not FDA-approved but used under an Emergency Use Authorization (EUA); outline the risks, benefits and document the conversation ● Direct facility staff to e-mail the Patient Fact Sheet to family, or print and give to family/patient ● Identify facility nurse (e.g., manager) who can track process, administer, ensure monitoring ● Order REGEN-COV from pharmacy for subcutaneous administration ○ Consider participating/helping on site, the first time or two at a given facility ● Do not order for patients who are hypoxic or ill enough to be hospitalized, even if the decision is made not to pursue hospitalization [See Appendix 1] ● Report any adverse events to FDA [See Appendix 4]

Appendix 1 - General Information about Monoclonal Antibodies/REGEN-COV for COVID-19 and use in congregate living

- **What is REGEN-COV/monoclonal antibodies for COVID-19**
  - Casirivimab 600 mg and imdevimab 600 mg = recombinant human IgG1 monoclonal antibodies targeting the spike protein of SARS-CoV-2. Brand name "REGEN-COV"
  - Authorized under EUA November 21, 2020
  - For the treatment of mild to moderate disease in persons at high risk of progression to severe disease

- **Benefit**
  - Significant reduction in hospitalization and death, especially older and high-risk persons
    - Most recent study Mayo Clinic, August 30, 2021 https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00382-5/fulltext
    - Table with relevant studies as of August 4, 2021 in NIH COVID-19 Treatment Guidelines https://healthpolicy.duke.edu/publications/covid-19-monoclonal-antibody-treatments-using-evolving-evidence-improve-care-pandemic
    - Earlier summary of evidence https://healthpolicy.duke.edu/publications/covid-19-monoclonal-antibody-treatments-using-evolving-evidence-improve-care-pandemic

- **Indication**
  - Mild to moderate disease
    - Not hospitalized
    - Not hypoxic due to COVID-19; see Limitations in next section
  - Can be used for post-exposure prophylaxis, but the focus in this document is on early treatment of symptomatic persons
  - Requires positive direct viral test (PCR, NAAT, or Antigen test)

- **Limitations of benefit and potential for risk in patients with severe COVID-19**
  - May be associated with worse clinical outcomes when administered to hospitalized patients
  - Not authorized for use in patients who
    - Are hospitalized due to COVID-19
    - Require oxygen therapy due to COVID-19
    - Require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen for other reasons

- **Eligibility**
  - Persons at high risk for progression (nearly all SNF/ALF patients qualify)
    - Age 65 and older
    - Chronic lung disease
    - Cardiovascular disease or hypertension
    - Diabetes
    - Obesity (BMI>25)
    - Chronic kidney disease
    - Immunosuppressive disease or immunosuppressive treatment
    - Cancer
    - Sickle cell disease
    - Medical-related technological dependence (tracheostomy, gastrostomy, etc.)
    - Neurodevelopmental disorders or other medical complexity
    - ***Clinical judgment on the part of the medical provider for persons not in the above categories***
    - 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

- Impact of vaccination status
  - Does not affect eligibility; people who are vaccinated may receive if otherwise eligible
  - After receiving monoclonal antibody treatment, it is recommended to wait 90 days for further COVID-19 vaccination, but monoclonal antibody treatment may be given within 90 days of receiving a vaccination
- At least 40 kg
- No adjustment for renal impairment

- **Timing**
  - As soon as possible after positive viral test in patients with symptoms, but must be within 10 days of symptom onset
  - If test positive - but no symptoms identified yet - consider treatment with REGEN-COV based on clinical judgment and shared decision-making with patient and/or family
    - Can be difficult to assess symptoms in some congregative living residents due to dementia and other factors
    - Can be difficult to identify later onset of symptoms if initially symptom-free, in congregate living settings

- **Administration**
  - IV preferred, **subcutaneous is an alternative if IV not feasible or would delay treatment**
    - This currently applies to most patients in congregate living settings

- **Subcutaneous administration**

Preparation of 600 mg of Casirivimab and 600 mg of Imdevimab for Subcutaneous Injections	
Formulation	**Preparation of 4 Syringes**
Casirivimab and Imdevimab **Co-formulated** vial	Withdraw 2.5 mL solution per syringe into FOUR separate syringes
Casirivimab and Imdevimab **Individual** vials	**Casirivimab**: Withdraw 2.5 mL solution into TWO syringes. **Imdevimab**: Withdraw 2.5 mL solution into TWO syringes. For a total of FOUR syringes.

APPENDIX 2. Further Information for Long-Term Care Pharmacies

- **Medication comes from AmerisourceBergen; it is provided free (paid for by U.S. government) from the distributor. Order form:**
  - C19 Therapies Request Form
    - https://app.smartsheet.com/b/form/255d164d67834793b4ab549e160941e8

- **May come in one of two forms:**
  - One 10 ml vial of 1:1 mixture casirivimab 600 mg + imdevimab 600 mg
    or
  - Individual vials, two of casirivimab and two of imdevimab

- **Storage**
  - Refrigerate per package instructions
  - Shelf life refrigerated is approximately 1 year, before vial punctured
  - In syringes or once punctured, must be used within 4 hours

- **Deliver to facilities via stat delivery if possible**
  - Keep at refrigerated temperature during transport

- **Coordinate with facility to determine who will receive the medication**
  - They should refrigerate, if not going to administer immediately

- **Coordinate with facility where supplies for administration, and anaphylaxis medications/e-kit, will come from**
  - Supplies including four 3- or 5-ml syringes, four 21 g 1.5-inch drawing-up needles, and four 25 or 27 g administration needles
  - Anaphylaxis e-kit including EpiPen, Benadryl (IM or oral)

Appendix 3. Further Information for Long-Term Care and Assisted Living Facilities

Monoclonal Antibody Treatment for Patients with Active COVID-19 REGEN-COV

- Consider limiting to Monday-Friday, daytime hours, when staffing is sufficient, pharmacies are fully operating, and patients' primary care team is available

- Contraindication to REGEN-COV:
  - Previous severe hypersensitivity reactions, including anaphylaxis, to REGEN-COV

- Comes from pharmacy usually in one 10 ml vial
  - Mixture of 600 mg casirivimab and 600 mg imdevimab
  - May come in individual vials (two separate medications, two vials each)
  - Keep refrigerated until 20 minutes prior to use

- Patient/Family/Surrogate must be given the patient fact sheet; find the latest version: https://www.fda.gov/media/145612/download

Subcutaneous Administration:

- **Miscellaneous preparation**
  - Encourage oral hydration before and after administration
  - Additional staff may be needed to assist with patients with dementia, or assistance with repositioning for injection to different locations, etc.

- **Supplies needed**
  - 4 syringes (3 or 5 ml)
  - 21-gauge 1.5-inch transfer needle
  - Four 25- or 27-gauge needles
    - 25 gauge may be preferred due to viscosity (thickness) of the liquid
    - 23 gauge has been noted to be easier by some users
  - Medications that must be on hand in case of anaphylaxis
    - EpiPen
    - Benadryl
  - Gloves
  - Alcohol wipes
  - Ensure whether these supplies and anaphylaxis e-kit will be sent from pharmacy, or if they are already in your facility

- **Drawing up**
  - Remove from refrigerated storage and allow to come to room temperature 20 minutes prior to use
  - Do not shake or expose to heat
  - Inspect for particulate matter or discoloration (should be clear and colorless to pale yellow)
  - Withdraw 2.5 ml of solution into each of four syringes
    - If dispensed as 2 separate medications, withdraw 2.5 ml of each drug x 2 syringes each
  - Replace 21 g drawing-up needle with 25 g or 27 g needle for administration

- **Administering Subcutaneously**
  - Administer the subcutaneous injections consecutively in 4 different sites
  - Thigh, back of upper arm, abdomen, except 2" around navel; avoid waistline
  - Avoid skin that is tender, damaged, bruised, or scarred

- The prepared syringes may be stored under refrigeration at 2 º to 8 º c (36 º to 46 º F) for no more than 4 hours or at room temperature up to 25 º C (77 º F) for no more than 4 hours
- If IV administration is feasible, review instructions here https://www.fda.gov/media/145611/download

- **Monitoring for hypersensitivity reactions**
  - Keep in visual contact for one hour after administration
    - Can be clinical staff, or other staff who can notify clinical staff if symptoms noted
  - Similar to post-covid-vaccine monitoring/observation
  - Thorough assessment including VS if change in condition
    - And notify ordering provider
  - Symptoms and signs of hypersensitivity (anaphylaxis and infusion reactions) can include:
    - Angioedema
    - Rash including urticaria
    - Fever and chills
    - Difficulty breathing, bronchospasm
    - Chest pain or discomfort
    - Nausea or vomiting
    - Weakness
    - Altered mental status
    - Pruritus
    - Syncope
    - Dizziness
    - Vasovagal reactions
    - Myalgias
    - Throat irritation
    - Hypotension
    - Arrhythmia
  - Medications to have on hand in case of anaphylaxis-type reaction
    - Epinephrine (EpiPen)
    - Diphenhydramine (IM or oral)
  - Reactions are rare. Most within 1 hour; can occur up to 24 hours later (even more rare)
  - Review facility procedure for identifying and managing anaphylaxis
    - Not all reactions will meet criteria for anaphylaxis/require epinephrine
    - Be able to identify, administer EpiPen, and call 911 per facility procedure
  - Notify provider of any reaction or change in condition

- **Information from Regeneron about reactions with subcutaneous administration**
  - Injection site reactions occurred in 12% and 4% of subjects following single dose administration in the REGEN-COV and placebo groups, respectively.
  - Remaining safety findings following subcutaneous administration in the REGEN-COV group were similar to the safety findings observed with intravenous administration....
  - Hypersensitivity reactions occurred in 8 subjects (1%) in the REGEN-COV group; and all hypersensitivity reactions were grade 1 or 2 in severity. There were no cases of anaphylaxis.

- **Continue COVID-19 isolation and monitoring**
  - Clinical worsening - notify provider

- **Billing for administration -** Per CMS:

Payment Allowances and Effective Dates for COVID-19 Monoclonal Antibodies and their Administration During the Public Health Emergency

CPT Code or HCPCS Code	CPT or HCPCS Short Descriptor	Labeler Name	Vaccine/Procedure Name	National Payment Allowance Effective for Claims with DOS on or after 03/15/2021	National Payment Allowance Effective for Claims with DOS through 03/14/2021	Effective Dates
M0243	Casirivi and imdevi inj	Regeneron	Intravenous infusion or subcutaneous injection, casirivimab and imdevimab includes infusion or injection, and post administration monitoring	$450.00[3]	$309.600[3]	11/21/2020 – TBD

Source: https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/covid-19-vaccines-and-monoclonal-antibodies
As of September 10, 2021

Appendix 4. Further Information for Medical Providers

Determining use:

- See background information Appendix 1
- Provider fact sheet https://www.fda.gov/media/145611/download
- Use clinical judgment about use/who may benefit
    - Do not order for patients who are hypoxic or ill enough to be hospitalized, even if the decision is made not to pursue hospitalization

After determining eligibility but before ordering:

- Conversation with patient or (more likely) family member/POA, to include
    - Reasons for REGEN-COV use
    - Under EUA (Emergency Use Authorization)
    - Eligibility
    - That they can accept or decline
    - Potential risks and benefits
    - Alternative treatments (there are none)
    - Ongoing need for isolation precautions and infection control
    - Delay of future COVID-19 vaccination doses, if applicable

- Provide a copy of "Fact Sheet for Patients, Parents and Caregivers"
    - https://www.fda.gov/media/143893/download
    - E-mail to facility and direct them to e-mail to family
      -or-
    - Have facility print copies and provide directly to patient/family

- Ordering REGEN-COV from pharmacy
    - Write on order sheet as per usual unless different requirement
    - See pharmacy spreadsheet – a few require their own form be filled out
    - Fax to pharmacy, or facility fax to pharmacy

- Ordering provider and/or medical director may consider assisting on-site, or being present, the first time or two this is administered in facility
    - Provides assurance and collaboration to facility staff
    - Also provides reassurance to patient/family
    - Learning opportunity for all involved

- Remain involved during the process (if on-site or off-site)
    - Have facility confirm with you when medication delivered and administered, and after 1 hour observation period complete
    - Also check in after 24 hours to see whether any later reactions occur
    - Continue to track patient's status/symptoms

AFTER administration:

- Patient continues isolation (minimum 10 days), continue monitoring VS and clinical status
    - Clinical worsening - consider higher level of care depending on goals of care

- PROVIDER must submit report on all adverse, life-threatening events to FDA MedWatch
    - Serious adverse reactions:
        - Death
        - Life-threatening adverse event

        - Hospitalization
        - Persistent or significant incapacity or substantial disruption of ability to conduct normal life functions
        - Medical or surgical intervention to prevent death, life-threatening event, hospitalization, or disability
    - Call 1-800-FDA-1088 or www.fda.gov/medwatch/report.htm
    - In field “Event, problem, or product use/medication error” put “REGEN-COV use for COVID-19 under EUA”
    - Also inform Regeneron Pharmaceuticals: medical.information@regeneron.com

- If post-exposure prophylaxis considered, review in Provider Fact Sheet https://www.fda.gov/media/145611/download

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Minnesota Association of Geriatrics Inspired Clinicians https://www.minnesotageriatrics.org/

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