These Clinical Guidelines have been created by CarepathRx solely for its internal use and the use of its contracted clinical partners. All other use of these Guidelines is prohibited without express written permission. Published as Clinical Guidelines, CarepathRx's clinical partners may adopt these as policies subject to the partner's policy adoption processes.

These Clinical Guidelines have been created using resources that were current as of the "Reviewed" date noted at the beginning of the document. Clinicians should refer to the manufacturer's Prescribing Information (or equivalent) for the most up-to-date information. While CarepathRx has published these Clinical Guidelines after a close review of available literature and a clinical review process, given the evolving nature and complexity of modern pharmaceutical products, CarepathRx does not and cannot warrant or guarantee that these Clinical Guidelines reflect the objectively best or highest standard of care at any given time.

Nothing within these Clinical Guidelines is intended to supersede or interfere with any individual clinician's decision-making or professional judgment with respect to either (1) prescribing or dispensing the drug or product in question or (2) the overall treatment plan for an individual patient.

CAREPATHrx™
Specialty Pharmacy & Infusion Solutions

CLINICAL GUIDELINES FOR INTRAVENOUS REMEDESIVIR FOR THE TREATMENT OF COVID-19 IN AN OUTPATIENT SETTING

Section: Nursing
Compliance: Infusion Pharmacy
ACHC Standards: N/A
URAC Standards: N/A
Policy ID: NUR251
Effective: 12/1/2022
Reviewed:
Revised:
Approved by: Kathleen Patrick, President, 12/1/2022

I. BACKGROUND

Remdesivir (Veklury®) is approved by the U.S. Food and Drug Administration (FDA) for adults and pediatric patients (28 days of age and older and weighting at least 3 kg) with positive results of direct SARS-CoV-2 viral testing for the treatment of COVID-19 in a hospital or outpatient setting who are at high risk of progressing to severe COVID-19 and/or hospitalization. For the purposes of this guideline, first dose criteria include patients who are 18 years of age or older and who weigh 40 kg or more. Patients 28 days of age and older and weighing 3 kg or more may receive subsequent doses in the home as long as their first dose in the clinic was well-tolerated.

Remdesivir is an inhibitor of the SARS-CoV-s RNA-dependent RNA polymerase (RdRp), which is essential for viral replication. Remdesivir is an adenosine nucleotide prodrug that is metabolized to the pharmacologically active nucleoside triphosphate metabolite after being distributed into cells. Remdesivir triphosphate acts as an adenosine triphosphate analog and compete for incorporation into RNA chains by the SARS-CoV-2 RdRp, resulting in delayed chain termination during viral RNA replication. Remdesivir triphosphate can also inhibit viral RNA synthesis due to incorporation into the viral RNA template. The following outlines the procedures for servicing patients in need of outpatient Remdesivir home infusion.

II. PATIENT ACCEPTANCE CRITERIA

A. All patients referred for outpatient remdesivir therapy shall meet high-risk criteria per published guidelines and/or institutional policy. The treatment course should be initiated as soon as possible after diagnosis and within 7 days of symptom onset. Patients should be 28 days of age or older and weigh at least 3 kilograms (kg). Pediatric first doses will be required to be administered in a clinic. Subsequent doses may be administered in the home. The decision to administer a course of remdesivir infusion in the home will be determined on a case-by-case basis and reviewed by nursing and pharmacy management in conjunction with the referring provider.

B. Onboarding information for home treatment of COVID-19 with remdesivir will include:

1. Allergy profile, including history of anaphylactic reaction
2. Other relevant social and/or medical history
3. Current medication profile confirming patient is not currently prescribed chloroquine phosphate or hydroxychloroquine sulfate, and that no other contraindications exist. Interaction checker available at https://www.covid19-druginteractions.org/checker
4. Contact information for prescribing office
5. Contact information for contracted nursing agency
6. Necessity of baseline labs will be determined at the discretion of the provider. Hepatic, renal and prothrombin time laboratory testing before and during treatment is recommended by the manufacturer.

C. Physician orders for intravenous remdesivir must include:
1. Patient weight (estimate is acceptable)
2. Drug, dose, frequency
3. Route of administration (IV)
4. Ana-kit per protocol (required for all patients)
5. Peripheral line insertion and post-treatment removal, if applicable
6. Routine line care orders (maintenance, PRN)
7. Dispensing pharmacy treatment protocol for anaphylaxis will be instituted unless a more comprehensive patient-specific order is provided by physician. See policy NUR012 or Appendix A.

***Physician prescribing "Remdesivir – Outpatient Kit per Protocol" will meet all these prescription items.**

III. PHARMACOLOGY OVERVIEW

Refer to manufacturer's full Prescribing Information for most up to date information.

A. Indications for intravenous administration
1. Treatment of COVID-19 in adults and pediatric patients (28 days of age and older, weighing at least 3kg) with positive results of direct SARS-CoV-2 viral testing, who are not hospitalized, and have mild to moderate COVID-19 and are high-risk for progression to severe COVID-19, including hospitalization or death.
2. Remdesivir can be given via peripheral or central intravenous access
3. The recommended total treatment duration for non-hospitalized patients is 3 days.

B. Dosage
1. Adults and pediatric patients weighing at least 40kg:
    a. A single loading dose of Remdesivir 200mg on Day 1 via intravenous infusion followed by once-daily maintenance doses of Remdesivir 100mg starting Day 2 via intravenous infusion
2. Pediatric patients 28 days of age and older, and weighing 3kg to less than 40kg:
    a. A single loading dose of Remdesivir 5mg/kg on Day 1 via intravenous infusion followed by once-daily maintenance doses of Remdesivir 2.5mg/kg from Day 2 via intravenous infusion. CarepathRx advises pediatric patients weighing less than 40kg receive a loading dose in a controlled, outpatient infusion setting

3. Renal impairment
    a. No dose adjustment. Use has not been evaluated in patients with renal impairment. Because the excipient betadex sulfobutyl ether sodium is renally cleared and accumulates in patients with decreased renal function, administration of drugs formulated with betadex sulfobutyl ether sodium (such as remdesivir) is not recommended in patients with eGFR less than 30mL/m
4. Hepatic impairment
    a. No dose adjustment. Use has not been evaluated.

C. Contraindication
1. Patients with a history of clinically significant hypersensitivity reactions to remdesivir or any components of the product

D. Warnings and precautions
1. Hypersensitivity reactions, including infusion-related and anaphylactic:
    a. Hypersensitivity reactions, including infusion-related and anaphylactic reactions, have been observed during and following administration of remdesivir; most occurred within one hour.
    b. Signs and symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering.
    c. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. Monitor patients during infusion and observe patients for at least one hour after infusion is complete for signs and symptoms of hypersensitivity as clinically appropriate. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of remdesivir and initiate appropriate treatment.
2. Increased risk of transaminase elevations:
    a. Transaminase elevations have been observed in healthy volunteers who received 200mg of remdesivir followed by 100mg doses for up to 10 days; the transaminase elevations were mild (Grade 1) to moderate (Grade 2) in severity and resolved upon discontinuation of therapy. Transaminase elevations have also been reported in patients with COVID-19 who received remdesivir. Because transaminase elevations have been reported as a clinical feature of COVID-19, and the incidence was similar in patients receiving placebo versus remdesivir in clinical trials, discerning the contribution of treatment to transaminase elevations in patients with COVID-19 can be challenging.
3. Risk of reduced antiviral activity when co-administered with chloroquine phosphate or hydroxychloroquine sulfate:
    a. Co-administration of remdesivir and chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on data from cell culture experiments demonstrating a potential antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of remdesivir.
4. Pregnancy
    a. Available data from published case reports and compassionate use of

remdesivir in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In nonclinical reproductive toxicity studies, remdesivir demonstrated no adverse effect on embryo-fetal development when administered to pregnant animals at systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) that were 4 times (rats and rabbits) the exposure in humans at the recommended human dose (RHD) (see Data). There are maternal and fetal risks associated with untreated COVID-19 in pregnancy. A pregnancy exposure registry has been created that monitors pregnancy outcomes in individuals exposed to remdesivir during pregnancy.

b. Pregnant and recently pregnant individuals can go to https://covid-pr.pregistry.com to enroll or call 1-800-616-3791 to obtain information.

E. Adverse reactions

1. The most common adverse reactions (incidence ≥5%, all grades) observed with treatment with remdesivir are nausea, and increased ALT/AST. Other reactions identified during use under Emergency Use Authorization (EUA) include administration site extravasation, rash, anaphylaxis, angioedema, infusion-related reactions, hypersensitivity.
2. Post-marketing reports of bradycardia, including severe bradycardia and sinus bradycardia have been reported in patients receiving remdesivir for COVID-19. An observational study using data from the WHO pharmacovigilance database found that bradycardia was more likely to be reported with remdesivir treatment than with hydroxychloroquine, lopinavir/ritonavir, tocilizumab, or glucocorticoid treatment, and reports included mostly males in the United States over a wide spectrum of ages (43 to 79 years of age). Most of these patients were not receiving concurrent cardiovascular medications. Other cardiac effects were observed, most notably hypotension.

F. Pharmacokinetics

1. Pharmacokinetic differences based on sex, race, age, renal function, and hepatic function on the exposures of remdesivir were evaluated using population pharmacokinetic analysis. Sex and race did not affect the pharmacokinetics of remdesivir and its metabolites.

Table 12 Pharmacokinetic Properties of Remdesivir and Metabolites (GS-441524 and GS-704277)

	Remdesivir	GS-441524	GS-704277
Absorption			
T_{max} (h)[a]	0.67-0.68	1.51-2.00	0.75-0.75
Distribution			
% bound to human plasma proteins	88-93.6[b]	2	1
Blood-to-plasma ratio	0.68-1.0	1.19	0.56
Elimination			
$t_{1/2}$ (h)[c]	1	27	1.3
Metabolism			
Metabolic pathway(s)	CES1 (80%) Cathepsin A (10%) CYP3A (10%)	Not significantly metabolized	HINT1
Excretion			
Major route of elimination	Metabolism	Glomerular filtration and active tubular secretion	Metabolism
% of dose excreted in urine[d]	10	49	2.9
% of dose excreted in feces[d]	ND	0.5	ND

ND=not detected

a. Remdesivir administered as a 30-minute IV infusion (Study GS-US-399-5505); range of median observed on Day 1 and Day 5 or 10.

b. Range of protein binding for remdesivir from 2 independent experiments show no evidence of concentration-dependent protein binding for remdesivir.

c. Median (Study GS-US-399-4231).

d. Mean (Study GS-US-399-4231).

G. Drug interactions

1. Due to potential antagonism based on data from cell culture experiments, concomitant use of remdesivir with chloroquine phosphate or hydroxychloroquine sulfate is not recommended. Remdesivir and its metabolites are in vitro substrates and/or inhibitors of certain drug metabolizing enzymes and transporters. Based on a drug interaction study conducted with remdesivir, no clinically significant drug interactions are expected with inducers of cytochrome P450 (CYP) 3A4 or inhibitors of Organic Anion Transporting Polypeptides (OATP) 1B1/1B3, and P-glycoprotein (P-gp).

IV. NURSING PROCEDURE

A. Supplies for addEASE administration my include, but are not limited to:

1. Alcohol swabs
2. Sodium chloride flushes
3. IV pole
4. IV administration set with in-line or add-on 0.2-micron filter
5. IV start kit
6. Gloves
7. Extensions
8. Peripheral IV catheter
9. IV injection cap
10. Anaphylaxis kit per protocol

B. Supplies for home mix administration may include, but are not limited to:

1. Syringes of normal saline
2. Alcohol swabs
3. Vials of remdesivir
4. 33cc luer lock syringes

5. 18-gauge needles
6. Bag of sodium chloride 0.9% 100mL
7. Sodium chloride flushes
8. IV pole
9. IV administration set with in-line or add-on 0.2-micron filter
10. IV start kit
11. Gloves
12. Extensions
13. Peripheral IV catheter
14. IV injection cap
15. Small sharps container
16. Anaphylaxis kit per protocol

C. How supplied & storage
    1. **100mg lyophilized POWDER (**NDC 61958-2901-2) is supplied as a single-dose vial containing a sterile, preservative-free white to off-white to yellow lyophilized powder. It requires reconstitution and further dilution prior to administration by intravenous infusion. **Preparation instructions below reflect use of lyophilized powder.** Store vials at room temperature (below 86º F) until use.
    2. **100mg/20mL (5mg/mL) SOLUTION** (NDC 61958-2902-2) is supplied as a single-dose vial containing a sterile, preservative-free, clear, colorless to yellow aqueous-based solution. It requires dilution prior to administration by intravenous infusion. Store vials at refrigerated temperature.

D. Compatibility
    1. Compatible with 0.9% normal saline. Compatibility with other intravenous solutions is not known.

E. Procedures
    1. Nursing must don PPE prior to entering the patient's home (PPE provided by institution unless noted)
        a. N-95 mask
        b. Face shield
        c. Gown
        d. Gloves
        e. Shoe covers (per clinician desire)
    2. All home participants must wear a mask during the entirety of the nurse's visit
    3. Wash hands
    4. Don gloves
    5. Obtain baseline vital signs
    6. Assess patency of venous access or establish new venous access prior to preparation of drug
    7. Counsel patient on warnings, precautions, and potential side effects including, but not limited to:
        a. Hypersensitivity reactions, including:
            i. Anaphylaxis
            ii. Infusion related reactions
            iii. Nausea
            iv. Angioedema
        b. Bradycardia

c. Increased risk of hepatic laboratory abnormalities or inflammation

8. Inform patients to notify their healthcare provider immediately in the event of a pregnancy; it is not known whether remdesivir can pass into breast milk
9. Provide the following documentation and review with the patient:
    a. Fact Sheet for Patient, Parents, and Caregivers – Remdesivir
10. Prepare product: **addEASE instructions**
    a. Assembly of Remdesivir 100mg/100mL addEASE system should occur in an aseptic environment
    b. To activate addEASE remdesivir:
        i. Position vial below bag. Fold container one third from top and squeeze firmly to force plug from spike into vial. Diluent will begin to fill Remdesivir vial. Repeat this process until vial is approximately half full. Do not over fill. Thoroughly mix to dissolve in vial. Repeat this procedure as necessary until the contents of the vial are completely dissolved.
        ii. Invert product and hold with vial positioned over the container as shown. Fold container one third from top and squeeze firmly to transfer Remdesivir solution from vial to container.
        iii. Visually inspect solution for any particulate matter or discoloration. Reconstitution instructions:
        iv. For 200mg dose, infuse two Remdesivir 100mg/100mL addEASE bags back-to-back.

11. Prepare product: **home mix instructions**
    a. Each Remdesivir vial contains 100mg, available as a sterile, preservative-free, white to off-white to yellow lyophilized powder in single-dose vial for reconstitution.
    b. Store vials below 30°C (below 86°F) in the original carton protected from light until required for use.
    c. Reconstitution instructions:
        i. Remove the required number of single-dose vial(s) from storage.
            1) 200mg loading dose = 2 vials
            2) 100mg maintenance dose = 1 vial
        ii. Withdraw 19mL of 0.9% sodium chloride from bag and inject into each remdesivir 100mg vial.
        iii. Discard the vial if a vacuum does not pull into the vial
        iv. Immediately shake the vial for 30 seconds. Allow the contents of the vial to settle for 2 to 3 minutes. A clear solution should result.
        v. If the contents of the vial are not completely dissolved, shake the vial again for 30 seconds and allow the contents to settle for 2 to 3 minutes. Repeat this procedure as necessary until the contents of the vial are completely dissolved. Discard the vial if the contents are not completely dissolved.
        vi. After reconstitution, each vial contains 100mg/20mL (5mg/mL) of remdesivir solution.
        vii. Reconstituted solution should be clear, colorless to yellow. Visually inspect solution for any particulate matter or discoloration.
        viii. Use reconstituted product immediately to prepare the diluted drug product.

1) For patients weighing 40kg or more receiving remdesivir 100mg:
    a) Withdraw 100mg/mL from one remdesivir vial and transfer to remaining ~80mL 0.9% sodium chloride. Resulting volume equals ~100mL. gently invert the bag 20 times to mix. DO NOT SHAKE.
2) For patients weighing 40kg or more receiving remdesivir 200mg:
    a) Withdraw 100mg/20mL (total volume 40mL) from two remdesivir vials and transfer to remaining ~60mL 0.9% sodium chloride. Resulting volume equals ~100mL. Gently invert the bag 20 times to mix. DO NOT SHAKE.
3) For pediatric patients 28 days of age and older, weighing 3kg to less than 40kg:
    a) Further dilute the 100mg/20mL (5mg/mL) remdesivir solution to a fixed concentration of 1.25mg/mL. Determine the total infusion volume needed to achieve a final infusion volume concentration of 1.25mg/mL solution based on the patient's calculated dose and infuse via bag or syringe using 0.9% sodium chloride injection for further dilution.

ix. Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration

x. Product must be infused within one hour of compounding when mixed in the home. Care should be taken during admixture to prevent inadvertent microbial contamination. As there is no preservative or bacteriostatic agent present in this product, it is always recommended to administer intravenous medication immediately after preparation when possible.

12. Begin infusion at prescribed rate
    a. Recommended infusion time is 30 to 120 minutes. Use administration tubing with 0.2-micron filter,
13. Obtain TPR (temperature, pulse, respiration) and BP (blood pressure):
    a. Baseline prior to the infusion starting
    b. During infusion, as needed, based on RN evaluation of the patient's response
    c. At the completion of the infusion and completion of the observation period (60 minutes post-infusion)
    d. Caregiver may be taught vital sign monitoring
14. In case of mild adverse reaction(s):
    a. Stop infusion until symptoms subside
    b. Resume infusion at slower rate
15. If reaction continues or increases:
    a. Stop infusion
    b. Administer emergency medications. Notify physician immediately. Patient may be transferred to emergency room or appropriate medical setting if necessary.

16. At the completion of the infusion, flush with 0.9% sodium chloride.
17. Confirm discontinuation of treatment following Day 3 infusion. Remove peripheral line or resume prior central catheter care, as applicable.
18. Document administration.

V. MONITORING

A. Monitor patients during infusion and observe patients for at least one hour after infusion is complete for signs and symptoms of hypersensitivity

B. Follow institutional protocol for post-treatment monitoring, if applicable. Recommendations may include:
   a. Telephone call attempt within 5 to 7 days of initial dose (post-treatment days 2 to 4) to assess for delayed reactions, signs/symptoms of adverse events.
   b. Confirmation of removal of vascular access device to discharge patient from service.

C. Adverse events attributed to remdesivir must be reported to Gilead Sciences, Inc. at 1-800-GILEAD-5 and FDA MedWatch (www.fda.gov/medwatch).
   a. Provide a submission of the event to Gilead: (Patient Safety Reporting (gilead.com)).

***Refer to manufacturer's full Prescribing Information for most up to date information**

REFERENCES:

Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 — final report. N Engl J Med 2020; 383:1813-1826.

Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe COVID-19 in outpatients. *N Engl J Med*. 2021.

The COVID-19 Treatment Guidelines Panel's Statement on Therapies for High-Risk, Non-hospitalized Patients with Mild to Moderate COVID-19. National Institute of Health. Updated December 30, 2021. Accessed January 7, 2022. Statement on Therapies for High-Risk, Nonhospitalized Patients | COVID-19 Treatment Guidelines (nih.gov)

Touafchia A, Bagheri H, Carrié D, Durrieu G, Sommet A, Montastruc F. Serious bradycardia and remdesivir for coronavirus 2019 (COVID-19): a new safety concern. Clin Microbiol Infect. Published online February 26, 2021. doi:10.1016/j.cmi.2021.02.013

Veklury [package insert]. Foster City, CA; Gilead; 2022 (veklury_pi.pdf (gilead.com))

APPENDIX A: ANAPHYLAXIS KIT INTRUCTIONS

Emergency Medication After Your Infusion

Please call your pharmacy if you have any questions or concerns. In the event of an emergency, always call 911.

Your nurse will tell you when you need to use Emergency Medications.
The epinephrine dose will be noted on the Anaphylaxis Protocol included with your kit.

Start with a clean work surface and clean hands.

Open the supply bag labeled Anaphylaxis Kit Contents.

You will need:

1. **Bag containing Pills** (2 Acetaminophen and 2 Diphenhydramine)
2. **Bag containing Alcohol Prep Pads**
3. **Bag labeled IM Epinephrine**

All other contents will not be needed.

Open the IM Epinephrine Bag

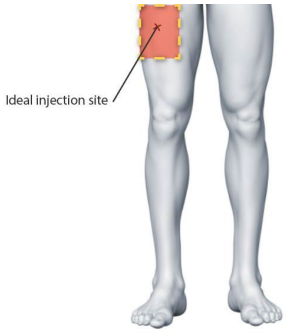
1. **Remove 1 of each item**
    a. 1 -syringe
    b. 1 – brown labeled filter needle (BD Filter Needle)- **for ampule use only**
    c. 1 – black labeled safety needle (Magellan Hypodermic Safety Needle 22G x 1”)
    d. 1 ampule of epinephrine

Prepare IM (intramuscular) injection of Epinephrine:

1. **Attach the brown filtered needle to syringe**
    a. Be careful to not touch the tip of the syringe or the needle.
2. Using an **alcohol swab, wipe the neck of the epinephrine ampule.**
3. Holding the ampule upright, **swirl and flick the ampule until all fluid flows to the bottom chamber** (the top chamber should be empty).
4. Using a new alcohol wipe, grasp the neck of the ampule and with your other hand grasp the bottom chamber of the ampule. **Quickly snap the top of the ampule off, directing the snap way from you.**
5. **Place the tip of the brown filter needle inside the ampule**. Tilting the ampule, **withdraw dose of medication into the syringe** by gently pulling back on the plunger. Be careful to not pull the plunger out of the syringe.

6. Remove the needle from the ampule and h**old the syringe upright** with the needle pointing upward. **Gently tap the side of the syringe to bring any air to the top of the syringe.**
7. **Push the air out of the syringe by gently pushing on the plunger**.
8. Replace the cap on the brown filter needle. Discard remainder in ampule.
9. **Remove the brown filter needle and place the black safety needle onto the syringe.**

Give your IM Epinephrine injection



1. **Grasp your leg muscle at the outer mid-thigh** and **cleanse the area** with a new alcohol wipe.
2. **Push the needle into your leg muscle straight** in at a 90-degree angle.
3. **Inject the medication** by depressing the plunger in a slow and steady motion.
4. **Remove the needle** and wipe the site with the alcohol wipe.
5. May repeat dose every 5 minutes (**maximum 3 doses**) if ordered per protocol.

Take the pills by mouth.

a. 2 – Acetaminophen
b. 2 – Diphenhydramine

Place all trash in the bag the pills came in and take with you when you seek medical care. **Give the bag to the nurse or EMT**, so your doctor will know what medication you already took. They will properly dispose of the syringe and needles.
Call 911 or have someone drive you to the emergency department.