HAWAIʻI PACIFIC HEALTH | KAPIʻOLANI PALI MOMI STRAUB WILCOX

CREATING A HEALTHIER HAWAIʻI

Hawai'i Pacific Health COVID-19 Treatment Protocol

Last updated 08 05 20

ID consult is required for:

- Hospitalized patients who have tested positive for COVID-19
- Prescribing of remdesivir, COVID-19 Convalescent Plasma (CCP) or any other investigational agent for the treatment of COVID-19 is restricted to ID approval

SMC	PMMC	WMC	KMCWC
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For drug or pharmacy-related questions, please contact your COVID pharmacist:

SMC	PMMC	WMC	KMCWC
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This is a living document that will be updated in real time as more data emerges. For questions on the treatment protocol or other COVID-19 drug treatment options, please contact:

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There are no FDA-approved therapies for the treatment of COVID-19. Clinical trial data is rapidly emerging and national guidelines are being updated frequently. The decision to treat patients should involve clinical judgment and shared decision making. When available, clinical trials are preferred.

National Institutes of Health (NIH) COVID-19 Treatment Guidelines:
https://www.covid19treatmentguidelines.nih.gov/

Infectious Diseases Society of America (IDSA) Guidelines on the Treatment and Management of Patients with COVID-19: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

Management of patients with COVID-19 at Hawai'i Pacific Health

Post-Exposure Prophylaxis	- No current recommendation for specific therapy outside the context of a clinical trial
Outpatient	- Supportive care only - No current recommendation for specific therapy outside the context of a clinical trial
Inpatient, SpO2 >94% on room air	- Supportive care only - Recommend against remdesivir, dexamethasone, and CCP
Inpatient, SpO2 ≤ 94% on room air, OR Requiring supplemental oxygen, OR Mechanical ventilation ≤72 hours	- Supportive care - Recommend remdesivir, dexamethasone, and CCP (if supply available)
Inpatient, Mechanical ventilation >72 hours, OR ECMO	- Supportive care - Recommend dexamethasone and CCP (if supply available) - Recommend against remdesivir

HPH COVID order sets: *COVID-19 Labs/Monitoring – HPH*
COVID-19 Orderset – HPH

*FDA Emergency Use Access (EUA) supply of remdesivir is available in limited quantities across the state. Contact Dr. Doug Kwock to obtain drug for an eligible patient. For patient criteria, EUA requirements etc., visit the FDA EUA Fact Sheet for Health Care Providers at https://www.fda.gov/media/137566/download or refer to Appendix B - *HPH Summary - FDA EUA of Remdesivir*.
*For pregnant women or pediatric patients less than 18 years old, remdesivir may also be obtained through Gilead's Compassionate Use program. Refer to *HPH Instructions - Compassionate Use Request for Remdesivir* and visit https://rdvcu.gilead.com/ for more information.
^CCP available through Expanded Access Program. Contact Dr. Wade Kyono for enrollment information (808)783-4501. Visit https://www.uscovidplasma.org for more study information, or refer to *COVID-19 Plasma EAP* on the HPH intranet.

Pregnancy considerations: MFM consult required for hospitalized confirmed pregnant COVID-19 patients; informed shared decision-making requires counseling regarding balancing maternal and fetal risk/benefit. Remdesivir should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus. Imaging: CT requires OB/MFM to discuss risk/benefits with patient prior to CT scan. Labs: During pregnancy lab values may be harder to interpret (e.g. D-dimer and fibrinogen typically elevated; Hgb/Hct, Cr, ferritin typically lower. "Normal" values for non-pregnant individuals (e.g. HCT 40, Cr of 1.0) can be considered elevated and may represent laboratory evidence of preeclampsia. It is critical to work with OB/MFM team to interpret laboratory values in pregnancy to prevent missing abnormal laboratory values that may appear "normal" to clinicians who typically work with non-pregnant adults.

Antiviral Agents

Agent	Adult Dose	Pediatric Dose	Main Toxicities	Notes
Remdesivir Mechanism: Inhibition of RNA synthesis	≥40kg: 200mg IV on Day 1, then 100mg IV q24h on Days 2-5. May use lyophilized powder or injection solution	3.5-<40kg: 5mg/kg IV on Day 1, then 2.5mg/kg IV q24h on Days 2-5. Lyophilized powder only	Infusion-related reactions, transaminase elevations, risk of reduced antiviral activity when coadministered with chloroquine or hydroxychloroquine	Due to limited supply, HPH criteria for use differs from FDA EUA criteria for use. Required labs, baseline & daily while on remdesivir: - Adults/peds >28 days: eGFR - Full term neonates (7-28 days old): SCr - All patients: Hepatic labs Recommendations for special populations: - Pregnancy: Use only if potential benefit > potential risk to mother and fetus - Renal impairment: Not recommended in adult and pediatric patients >28 days with eGFR <30ml/min or in full term neonates (7-28 days old) with SCr ≥1 mg/dl unless potential benefit > potential risk - Hepatic impairment: Do not initiate if ALT ≥5x ULN at baseline. Discontinue if ALT ≥5x ULN during treatment (may restart when ALT <5x ULN) or ALT elevation accompanied with s/sx liver inflammation or increasing conjugated bili, alk phos, or INR. Required EMR documentation – use *.remdesivir* smartphrase Required RL reporting for all medication errors and adverse events Drug administration: - Patient on Tele status - Infuse over 2 hours - Check BP/HR at baseline, q15min x 2, q30min x 2. Call physician for SBP<90 or HR<60. - Categorized as a Table 2 hazardous drug -Requires dual sign off on MAR

Supporting Agents

Agent	Adult Dose	Pediatric Dose	Main Toxicities	Notes
COVID-19 Convalescent Plasma (CCP) Mechanism: Neutralizing antibodies may provide short-term passive immunity	Per study protocol.	Peds are excluded from the study protocol.	Risks associated with the administration of plasma include allergic reactions and viral infections.	Efficacy and safety of COVID-19 convalescent plasma for the treatment of COVID-19 is not established. HPH is currently participating in a national CCP Expanded Access Program coordinated by the FDA and the Mayo Clinic.
Dexamethasone Mechanism: May prevent extended cytokine response; may promote resolution of inflammation in pneumonia	6mg IV/PO q24h x 10 days; discontinue upon discharge. Pregnant women: Consult MFM. If gestational age 23-36 weeks, consider 6mg IM q12h x 4 doses or until delivery, whichever is sooner. If dex is continued post-partum, reduce dose to 6mg IV/PO daily to complete a 10-day course; discontinue upon discharge.	0.15mg/kg (max 6mg) IV/PO q24h x 10 days; discontinue upon discharge.	Inhibition of immune response, reduction in pathogen clearance, increased viral shedding.	The benefits and risks of corticosteroid therapy should be weighed carefully before use. If dexamethasone is unavailable, contact Pharmacy for alternatives. Equivalent dosing: dexamethasone 6mg = prednisone 40mg = methylprednisolone 32mg = hydrocortisone 160mg.
Tocilizumab (Actemra) Mechanism: IL-6 receptor antagonist; treats cytokine release syndrome (CRS)	400mg IV x 1. Consider additional dose 8-12 hours later if continued clinical decompensation. Max 2 doses.	8 mg/kg IV x 1. Max dose 400mg. Round up or down to nearest vial size if within 10% of ordered dose. Consider additional dose 12 hours later if continued clinical decompensation. Max 2 doses.	LFT abnormalities, local injection site reactions, increased risk of serious infections, including TB and invasive fungal infections as well as other opportunistic pathogens	Consider use in the setting of high clinical suspicion for CRS: - Ferritin > 600 ug/L - D-dimer > 1 mg/L - LDH > 250 U/L - Clinical decline with reasonable exclusion of concomitant bacterial or fungal infection Use recommended in CRS Grade 3 and Grade 4. Consider use in Grade 2. CRS Severity: Grade 1: Fever, with or without constitutional symptoms Grade 2: Hypotension responding to fluids; hypoxia

				responding to <40% FiO2
				Grade 3: Hypotension managed with one pressor; hypoxia requiring ≥40% FiO2
				Grade 4: Life-threatening consequences; urgent intervention needed
				Avoid in pregnancy

Other

Agent	Notes
Anticoagulants	There is increasing evidence that patients with severe COVID-19 develop a hypercoagulable state, which has been associated with poor outcomes (e.g., progressive respiratory failure, acute respiratory distress syndrome [ARDS], death). Early anticoagulation in these patients may reduce the risk of thrombotic complications and improve clinical outcomes. The International Society for Thrombosis and Haemostasis, American College of Cardiology, and American Society of Hematology recommend that all hospitalized COVID-19 patients receive prophylactic-dose LMWH unless contra-indicated (e.g., active bleeding, severe thrombocytopenia, fibrinogen <0.5 g/L).
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	Currently no compelling evidence to support an association between ibuprofen and negative outcomes in patients with COVID-19. However, some experts have recommended preferentially using acetaminophen for treatment of fever. NIH COVID-19 Treatment Guidelines states that patients who are receiving NSAIDs for other conditions should continue receiving the drugs; states antipyretic strategy (e.g., use of acetaminophen or NSAIDs) should be no different between patients with or without COVID-19.
Angiotensin Converting Enzyme Inhibitors (ACE-Is) / Angiotensin II Receptor Blockers (ARBs)	Data are lacking; no evidence of harm or benefit with regards to COVID-19 infection. American Heart Association (AHA), American College of Cardiology (ACC), Heart Failure Society of America (HFSA), European Society of Cardiology (ESC) recommend to continue treatment with renin-angiotensin-aldosterone system (RAAS) antagonists in those patients who are currently prescribed such agents.
Statins	NIH COVID-19 Treatment Guidelines Panel states patients who are receiving a statin for the treatment or prevention of cardiovascular disease should continue statin therapy; recommends against use of statins for the treatment of COVID-19 except in the context of a clinical trial. In patients with active COVID-19 who may develop severe rhabdomyolysis, it may be advisable to withhold statin therapy for a short period of time.

References:

1. University of Washington ID Treatment Guidelines for SARS_CoV2. Accessed August 5, 2020. Available at: https://covid-19.uwmedicine.org/Pages/default.aspx.
2. ASHP Assessment of Evidence for COVID-19-Related Treatments. Accessed August 5, 2020. Available at: https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/ASHP-COVID-19-Evidence-Table.ashx.
3. NIH COVID-19 Treatment Guidelines. Accessed August 5, 2020. Available at: https://www.covid19treatmentguidelines.nih.gov/introduction/.
4. IDSA Guidelines on the Treatment and Management of Patients with COVID-19. Accessed August 5, 2020. Available at: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/.
5. FDA Fact Sheet for Health Care Providers – Emergency Use Authorization (EUA) of Remdesivir. Accessed August 5, 2020. Available at: https:// www.fda.gov/media/137566/ download.
6. Horby P, Lim WS, Emberson J et al. Effect of dexamethasone in hospitalized patients with COVID-19 – preliminary report. Available at: https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1. Accessed June 22, 2020.

Protocol revisions:

8/5/20: New table - Management of patients with COVID-19 at Hawai'i Pacific Health; added remdesivir notes; added dexamethasone alternatives and pregnancy dose; updated Appendices A & B; removed HCQ

6/24/20: Removed HCQ and Appendices A/B (HCQ monitoring and HCQ patient fact sheet); added dexamethasone

5/20/20: Added anticoagulants, new Appendix C Fact Sheet for Patients and Parents/Caregivers - FDA Emergency Use Authorization (EUA) of Remdesivir for COVID-19; new Appendix D – *HPH Summary - FDA EUA of Remdesivir*; HCQ no longer recommended outside the context of a clinical trial; updated remdesivir drug info

5/1/20: Added post-exposure prophylaxis section, CCP study protocol, concomitant medications section, new Appendix B HCQ Fact Sheet for Patients; removed Kaletra and AZM; amended inpatient algorithm, Actemra criteria for use

4/8/20: Added QTc monitoring for HCQ and AZM therapy and new Appendix A; updated peds HCQ dosing

4/3/20: Added outpatient treatment recommendations, pregnancy considerations, caution with HCQ-AZM combo therapy

3/27/20: Original version

Appendix A. Fact Sheet for Patients and Parent/Caregivers – FDA Emergency Use Authorization (EUA) of Veklury (remdesivir) for COVID-19.

Fact Sheet for Patients And Parents/Caregivers
Emergency Use Authorization (EUA) Of Veklury® (remdesivir) For Coronavirus Disease 2019 (COVID-19)

You are being given a medicine called **Veklury (remdesivir)** for the treatment of coronavirus disease 2019 (COVID-19). This Fact Sheet contains information to help you understand the potential risks and potential benefits of taking Veklury, which you have received or may receive.

There is no U.S. Food and Drug Administration (FDA) approved product available to treat COVID-19. Receiving Veklury may benefit certain people in the hospital with COVID-19. Read this Fact Sheet for information about Veklury. Talk to your healthcare provider if you have questions. It is your choice to receive Veklury or stop it at any time.

What is COVID-19?
COVID-19 is caused by a virus called a coronavirus. This type of coronavirus has not been seen before. You can get COVID-19 through contact with another person who has the virus.

COVID-19 illnesses have ranged from very mild (including some with no reported symptoms) to severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can happen and may cause some of your other medical conditions to become worse. Older people and people of all ages with severe, long-lasting (chronic) medical conditions like heart disease, lung disease, and diabetes, for example, seem to be at higher risk of being hospitalized for COVID-19.

What are the symptoms of COVID-19?
The symptoms of COVID-19 are fever, cough, and shortness of breath, which may appear 2 to 14 days after exposure. Serious illness including breathing problems can occur and may cause your other medical conditions to become worse.

What is Veklury (remdesivir)?
Veklury is an investigational antiviral medicine used for the treatment of certain people in the hospital with COVID-19. Veklury is investigational because it is still being studied. There is limited information known about the safety and effectiveness of using Veklury to treat people in the hospital with COVID-19. Veklury was shown in a clinical trial to shorten the time to recovery in some people. There are no medicines approved by the FDA as safe and effective to treat people in the hospital who have COVID-19. Therefore, the FDA has authorized the emergency use of Veklury for the treatment of COVID-19 under an Emergency Use Authorization (EUA). For more information on EUA, see the "**What is an Emergency Use Authorization (EUA)?**" section at the end of this Fact Sheet.

What should I tell my healthcare provider before I receive Veklury (remdesivir)?
Tell your healthcare provider about all of your medical conditions, including if you:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illnesses
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products). Veklury may affect the way other medicines work, and other medicines may affect how Veklury works.
  - **Especially tell your healthcare provider if you are taking the medicines chloroquine phosphate or hydroxychloroquine sulfate.**

How will I receive Veklury (remdesivir)?
Veklury is given to you through a vein (intravenous or IV) one time each day for up to 10 days depending on what your healthcare provider thinks is best for you. Veklury may help decrease the amount of the coronavirus in your body. This may help you to get better faster.

What are the important possible side effects of Veklury (remdesivir)?

Possible side effects of Veklury are:

- Allergic reactions. Veklury can cause allergic reactions, including serious reactions, during and after infusion. Tell your healthcare provider or nurse, or get medical help right away if you get any of the following signs and symptoms of allergic reactions: low blood pressure, changes in your heartbeat, shortness of breath, wheezing, swelling of your lips, face, or throat, rash, nausea, vomiting, sweating, or shivering.
- Increases in levels of liver enzymes. Increases in levels of liver enzymes have been seen in people who have received Veklury, which may be a sign of inflammation or damage to cells in the liver. Your healthcare provider will do blood tests to check your liver before you receive Veklury and daily while receiving Veklury.

These are not all the possible side effects of Veklury. Veklury is still being studied so it is possible that all of the risks are not known at this time.

Not a lot of people have taken Veklury. Serious and unexpected side effects may happen. The side effects of getting any medicine by vein may include brief pain, bleeding, bruising of the skin, soreness, swelling, and possible infection at the injection site.

What other treatment choices are there?

Like Veklury, FDA may allow for the emergency use of other medicines to treat people in the hospital with COVID-19. Go to https://www.covid19treatmentguidelines.nih.gov/ for information on the emergency use of other medicines that are not approved by FDA to treat people in the hospital with COVID-19. Your healthcare provider may talk with you about clinical trials you may be eligible for.

It is your choice to be treated or not to be treated with Veklury. Should you decide not to receive it or stop it at any time, it will not change your standard medical care.

What if I am pregnant or breastfeeding?

There is limited experience giving Veklury to pregnant women or breastfeeding mothers. For a mother and unborn baby, the benefit of receiving Veklury may be greater than the risk from the treatment. If you are pregnant or breastfeeding, discuss your options and specific situation with your healthcare provider.

How do I report side effects with Veklury (remdesivir)?

Tell your healthcare provider right away if you have any side effect that bothers you or does not go away.

Report side effects to **FDA MedWatch** at www.fda.gov/medwatch or call 1-800-FDA-1088.

How can I learn more?

- Ask your healthcare provider.
- Visit https://www.covid19treatmentguidelines.nih.gov/
- Contact your local or state public health department.

What is an Emergency Use Authorization (EUA)?

The United States FDA has made Veklury available under an emergency access mechanism called an EUA. The EUA is supported by a Secretary of Health and Human Service (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic.

Veklury has not undergone the same type of review as an FDA-approved or cleared product. FDA may issue an EUA when certain criteria are met, which includes that there are no adequate, approved, available alternatives. In addition, the FDA decision is based on the totality of scientific evidence available showing that it is reasonable to believe that the product meets certain criteria for safety, performance, and labeling and may be effective in treatment of patients during the COVID-19 pandemic. All of these criteria must be met to allow for the product to be used in the treatment of patients during the COVID-19 pandemic.

The EUA for Veklury (remdesivir) is in effect for the duration of the COVID-19 declaration justifying emergency use of these products, unless terminated or revoked (after which the products may no longer be used).

Reference:

1. Fact Sheet for Patients and Parents/Caregivers – Emergency Use Authorization (EUA) of Veklury (remdesivir) for Coronavirus Disease 2019 (COVID-19). Available at: https://www.fda.gov/media/137565/download. Accessed August 5, 2020.

Appendix B. HPH Summary – FDA EUA of Veklury (remdesivir).

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product Veklury (remdesivir, RDV) for treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in adults and pediatric patients hospitalized with severe disease.

Indications and Usage	Treatment of suspected or laboratory confirmed COVID-19 in adults and children hospitalized with severe disease. Severe disease is defined as patients with: - Oxygen saturation (SpO2) ≤ 94% on room air, - Requiring supplemental oxygen, - Requiring mechanical ventilation, or - Requiring extracorporeal membrane oxygenation (ECMO)
Dosage	<u>5-day regimen for patients NOT requiring mechanical ventilation and/or ECMO:</u> 3.5-<40kg: 5mg/kg IV on Day 1, then 2.5mg/kg IV q24h on Days 2-5. ≥40kg: 200mg IV on Day 1, then 100mg IV q24h on Days 2-5. If patient does not demonstrate clinical improvement, may extend treatment up to a total of 10 days. <u>10-day regimen for patients requiring mechanical ventilation and/or ECMO:</u> 3.5-<40kg: 5mg/kg IV on Day 1, then 2.5mg/kg IV q24h on Days 2-10. ≥40kg: 200mg IV on Day 1, then 100mg IV q24h on Days 2-10.
Special Populations	<u>Pregnancy:</u> No adequate and well-controlled studies of RDV use in pregnant women have been conducted. RDV should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus. In nonclinical reproductive toxicity studies, RDV demonstrated no adverse effect on embryofetal development when administered to pregnant animals at systemic exposures (AUC) of the predominant circulating metabolite of RDV (GS-441524) that were 4 times (rats and rabbits) the exposure in humans at the recommended human dose (RHD). <u>Breastfeeding:</u> There is no information regarding the presence of RDV in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies, RDV and metabolites have been detected in the nursing pups of mothers given RDV, likely due to the presence of RDV in milk. Because of the potential for viral transmission to COVID-19-negative infants and adverse reactions from the drug in breastfeeding infants, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RDV and any potential adverse effects on the breastfed child from RDV or from the underlying maternal condition. <u>Pediatric Use:</u> The safety and effectiveness of RDV for treatment of COVID-19 have not been assessed in pediatric patients. Dosing instructions for pediatric patients were derived based on pharmacokinetic data from adult healthy volunteers and *in vitro* data for RDV and other similar compounds, as part of the PBPK modeling and simulation approach which accounts for age-dependent changes in metabolism, distribution, and elimination of RDV.

	Geriatric Use: The pharmacokinetics of RDV have not been evaluated in patients >65 years of age. In general, appropriate caution should be exercised in the administration of RDV and monitoring of elderly patients, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Renal Impairment: The PK of RDV has not been evaluated in pts with renal impairment. All patients must have an eGFR determined before dosing. RDV is not recommended in adult and pediatric patients (>28 days old) with eGFR <30 mL/min or in full-term neonates (≥7 days to ≤28 days old) with SCr ≥1 mg/dL unless the potential benefit outweighs the potential risk. Hepatic Impairment: The PK of RDV has not been evaluated in pts with hepatic impairment. It is not known if dosage adjustment is needed in pts with hepatic impairment. RDV should only be used in pts with hepatic impairment if the potential benefit outweighs the potential risk. Hepatic laboratory testing should be performed in all pts prior to starting RDV and daily while receiving RDV.
Administration	See Appendices A & B - Administration and Preparation of Remdesivir for Adult and Pediatric Patients
Contraindications	Use in patients with known hypersensitivity to any ingredient of RDV
Warnings/ Precautions, Adverse Reactions	There are limited clinical data available for RDV. Serious and unexpected adverse events may occur that have not been previously reported with RDV use. Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed during and following administration of RDV. S/Sx may include hypotension, tachycardia, bradycardia, dyspnea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. If s/sx of a clinically significant hypersensitivity reaction occur, immediately discontinue administration and initiate appropriate treatment. Transaminase elevations have been observed in both healthy volunteers and patients with COVID-19. Hepatic laboratory testing should be performed in all patients prior to starting RDV and daily while receiving RDV. - RDV should not be initiated in patients with ALT ≥ 5 times the upper limit of normal at baseline - RDV should be discontinued in patients who develop ALT ≥ 5 times the upper limit of normal during treatment with RDV. RDV may be restarted when ALT is < 5 times the upper limit of normal, or ALT elevation is accompanied by s/sx of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR The following lab tests should be performed daily while receiving RDV: - Serum chemistries, hematology, ALT, AST, bilirubin, alk phos, SCr and CLcr

Drug Interactions	Coadministration of RDV and chloroquine or hydroxychloroquine is not recommended based on in vitro data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of RDV. Drug-drug interaction trials of RDV and other concomitant medications have not been conducted in humans. In vitro, RDV is a substrate for CYP2C8, CYP2D6, and CYP3A4, and is a substrate for Organic Anion Transporting Polypeptides 1B1 (OAPT1B1) and P-glycoprotein (P-gp) transporters. In vitro, RDV is an inhibitor of CYP3A4, OATP1B1, OATP1B3, BSEP, MRP4, and NTCP. The clinical relevance of these in vitro assessments has not been established.
Preparation	See Appendices A & B - Administration and Preparation of Remdesivir for Adult and Pediatric Patients
Storage	<u>Lyophilized Powder</u> Store RDV for injection, 100 mg, vials below 30°C (below 86°F) until required for use. Do not use after expiration date. The lyophilized powder must be reconstituted and diluted prior to use. After reconstitution, vials can be stored up to 4 hours at room temperature (68°F to 77°F) prior to administration or 24 hours at refrigerated temperature (36°F to 46°F). Dilute within the same day as administration. <u>Injection Solution</u> Store RDV injection, 5 mg/mL, vials at refrigerated temperature (2°C to 8°C [36°F to 46°F]) until required for use. Do not use after expiration date. Dilute within the same day as administration. Prior to dilution, equilibrate RDV injection to room temperature (20°C to 25°C [68°F to 77°F]). Sealed vials can be stored up to 12 hours at room temperature prior to dilution. The concentrated solution must be diluted prior to use. <u>Diluted Infusion Solution</u> Store diluted RDV solution for infusion up to 4 hours at room temperature (68°F to 77°F) or 24 hours at refrigerated temperature (36°F to 46°F). Do not reuse or save unused RDV lyophilized powder, injection solution, or diluted solution for infusion for future use. This product contains no preservative.
Dosage Forms	<u>RDV for injection, 100 mg:</u> Each single-dose vial of RDV for injection,100 mg, contains a sterile, preservative-free white to off-white to yellow lyophilized powder. <u>RDV injection, 100mg/20ml (5 mg/mL):</u> Each single-dose vial of RDV injection contains 5 mg/mL of RDV as a clear, colorless to yellow, aqueous-based concentrated solution.

Mandatory EUA Requirements for RDV Administration:

1. Treatment of suspected or laboratory confirmed COVID-19 in adults and children hospitalized with severe disease (see definition of severe disease in *Indications and Usage*). Specifically, RDV is authorized only for the following patients who are admitted to a hospital and under the care or consultation of a licensed clinician (skilled in the diagnosis and management of patients with potentially life-threatening illness and the ability to recognize and manage medication-related adverse events):
    a. Adult patients for whom use of an IV agent is clinically appropriate
    b. Pediatric patients for whom use of an IV agent is clinically appropriate
2. Prior to RDV administration (if clinically feasible), review and provide copy of FDA Fact Sheet for Patients and Parents/Caregivers. Fact sheet is available at: https://www.fda.gov/media/137565/download. Patient's medical record must include documentation that the patient/caregiver has been:
    a. Given the Fact Sheet for Patients and Parents/Caregivers,
    b. Informed of alternatives to receiving RDV, and
    c. Informed that RDV is an unapproved drug that is authorized for use under EUA.
    d. **Use smartphrase ".remdesivir" for documentation
3. Adult and pediatric patients (>28 days old) must have an eGFR determined and full-term neonates (≥7 days to ≤28 days old) must have serum creatinine determined prior to RDV first administration and daily while receiving RDV.
4. Hepatic laboratory testing should be performed in all patients prior to starting RDV and daily while receiving RDV.
5. Patients with known hypersensitivity to any ingredient of RDV must not receive RDV.
6. The prescribing health care provider and/or the provider's designee are/is responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of RDV.
7. The prescribing health care provider and/or the provider's designee are/is responsible for mandatory reporting of all medication errors and adverse events (death, serious adverse events*) considered to be potentially related to RDV occurring during RDV treatment within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "Remdesivir under Emergency Use Authorization (EUA)" in the description section of the report.
    a. *Serious adverse events are defined as: death; a life-threatening adverse event; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; a congenital anomaly/birth defect; a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.
    b. Submit adverse event reports to the FDA MedWatch using one of the following methods:
        i. Complete and submit report online: www.fda.gov/medwatch/report.htm, or
        ii. Call 1-800-FDA-1088 to request a reporting form
        iii. Submitted reports should include in the field name, "Describe Event, Problem, or Product Use/Medication Error", the statement "Remdesivir under Emergency Use Authorization (EUA)."

Administration and Preparation of Remdesivir (RDV) for Adults and Pediatric Patients Weighing ≥40kg.

Dose Administration

- The prepared diluted solution should not be administered simultaneously with any other medication. The compatibility of remdesivir injection with IV solutions and medications other than saline is not known.
- Administer the diluted solution with the infusion rate described in Table 1.
- After infusion is complete, flush with at least 30ml NS.

Table 1. Recommended Rate of Infusion — Diluted Remdesivir for Injection in Adults and Pediatric Patients Weighing ≥40 kg.

Infusion bag volume	Infusion time	Rate of infusion
250ml	30min	500 ml/hr
	60min	250 ml/hr
	120min	125 ml/hr

Dose Preparation

Remdesivir for Injection, 100mg, Lyophilized Powder

Reconstitution Instructions:

Remove the required number of single-dose vial(s) from storage. For each vial:

• Aseptically reconstitute remdesivir lyophilized powder by addition of 19 mL of Sterile Water for Injection using a suitably sized syringe and needle per vial.
• Discard the vial if a vacuum does not pull the Sterile Water for Injection into the vial.
• 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.
• 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.
• Following reconstitution, each vial contains 100 mg/20 mL (5 mg/mL) of remdesivir solution.
• Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
• After reconstitution, the total storage time before administration should not exceed 4 hours at room temperature or 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

Dilution Instructions:

Care should be taken during admixture to prevent inadvertent microbial contamination. As there is no preservative or bacteriostatic agent present in this product, aseptic technique must be used in preparation of the final parenteral solution. It is always recommended to administer IV medication immediately after preparation when possible.

• Using Table 2, determine the volume of 0.9% saline to withdraw from the infusion bag.

Table 2. Recommended Dilution Instructions— Remdesivir for Injection Lyophilized Powder in Adults and Pediatric Patients Weighing ≥40 kg.

Remdesivir dose	NS bag size	Volume of NS to be withdrawn and discarded from NS bag	Required volume of reconstituted remdesivir for injection
200mg	250ml	40ml	2 x 20ml

100mg	250ml	20ml	1 x 20ml

• Withdraw the required volume of saline from the bag using an appropriately sized syringe and needle. Discard the saline that was withdrawn from the bag.
• Withdraw the required volume of reconstituted remdesivir for injection from the remdesivir vial using an appropriately sized syringe per Table 3. Discard any unused portion remaining in the remdesivir vial.
• Transfer the required volume of reconstituted remdesivir for injection to the selected infusion bag.
• Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
• The prepared diluted solution is stable for 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 24 hours in the refrigerator at 2°C to 8°C (36°F to 46°F).

Remdesivir Injection, 100mg/20ml (5 mg/mL), Solution

Care should be taken during admixture to prevent inadvertent microbial contamination. As there is no preservative or bacteriostatic agent present in this product, aseptic technique must be used in preparation of the final parenteral solution. It is always recommended to administer IV medication immediately after preparation when possible.

Remove the required number of single-dose vial(s) from storage. For each vial:
• Equilibrate to room temperature (20°C to 25°C [68°F to 77°F]). Sealed vials can be stored up to 12 hours at room temperature prior to dilution.
• Inspect the vial to ensure the container closure is free from defects and the solution is free of particulate matter.
• Using Table 3, determine the volume of 0.9% saline to withdraw from the infusion bag.

Table 3. Recommended Remdesivir Solution Dilution Instructions in Adults and Pediatric Patients Weighing ≥40 kg.

Remdesivir Dose	NS bag size	Volume of NS to be withdrawn and discarded from NS bag	Required volume of remdesivir injection solution
200mg	250ml	40ml	2 x 20ml
100mg	250ml	20ml	1 x 20ml

• Withdraw the required volume of saline from the bag using an appropriately sized syringe and needle. Discard the saline that was withdrawn from the bag.
• Withdraw the required volume of remdesivir injection solution from the remdesivir vial using an appropriately sized syringe per Table 4.
• Pull the syringe plunger rod back to fill the syringe with approximately 10 mL of air.
• Inject the air into the remdesivir injection vial above the level of the solution.
• Invert the vial and withdraw the required volume of remdesivir injection solution into the syringe. The last 5 mL of solution requires more force to withdraw.
• Discard any unused solution remaining in the remdesivir vial.
• Transfer the required volume of remdesivir injection solution to the infusion bag.
• Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
• The prepared diluted solution is stable for 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 24 hours in the refrigerator at 2°C to 8°C (36°F to 46°F).

Administration and Preparation of Remdesivir (RDV) for Pediatric Patients 3.5kg-<40kg.

Dose Administration

- The prepared diluted solution should not be administered simultaneously with any other medication. The compatibility of remdesivir injection with IV solutions and medications other than saline is not known.
- Administer the diluted solution with the infusion rate described in Table 4.
- After infusion is complete, flush with a volume greater than the priming volume of the tubing to ensure the full dose is delivered.

Table 4. Recommended Rate of Infusion for Pediatric Patients Weighing 3.5 kg to <40kg.

Infusion bag volume	Infusion time	Rate of infusion
100ml	30 min	200 ml/hr
	60 min	100 ml/hr
	120 min	50 ml/hr
50ml	30 min	100 ml/hr
	60 min	50 ml/hr
	120 min	25 ml/hr
25ml	30 min	50 ml/hr
	60 min	25 ml/hr
	120 min	12.5 ml/hr

Dose Preparation

Remdesivir for Injection, 100mg, Lyophilized Powder

For pediatric patients with body weight between 3.5 kg and <40kg, use remdesivir for injection, 100mg, lyophilized powder only. This is due to the higher amount of SBECD present in the injection solution resulting in higher tonicity of the solution concentrate compared to the lyophilized formulation.

Reconstitution Instructions

Remove the required number of single-dose vial(s) from storage. For each vial:

• Aseptically reconstitute remdesivir lyophilized powder by addition of 19 mL of Sterile Water for Injection using a suitably sized syringe and needle per vial.
• Discard the vial if a vacuum does not pull the Sterile Water for Injection into the vial.
• 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.
• 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.
• Following reconstitution, each vial contains 100 mg/20 mL (5 mg/mL) of remdesivir solution.
• Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
• After reconstitution, the total storage time before administration should not exceed 4 hours at room temperature or 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

Dilution Instructions

- Care should be taken during admixture to prevent inadvertent microbial contamination. As there is no preservative or bacteriostatic agent present in this product, aseptic technique must be used in

preparation of the final parenteral solution. It is always recommended to administer IV medication immediately after preparation when possible.

- Following reconstitution as instructed above, each vial will contain a 100 mg/20 mL (5 mg/mL) remdesivir concentrated solution. For pediatric patients weighing 3.5 kg to less than 40 kg, the 100 mg/20 mL (5 mg/mL) remdesivir concentrate should be further diluted to a fixed concentration of 1.25 mg/mL using 0.9% sodium chloride.
- The total required infusion volume of the 1.25 mg/mL remdesivir solution for infusion is calculated from the pediatric weight-based dosing regimens of 5 mg/kg for the Loading Dose and 2.5 mg/kg for each Maintenance Dose.
- Small 0.9% sodium chloride infusion bags (e.g., 25, 50, or 100 mL) or an appropriately sized syringe should be used for pediatric dosing. The recommended dose is administered via IV infusion in a total volume dependent on the dose to yield the target remdesivir concentration of 1.25 mg/mL.
- A syringe may be used for delivering volumes less than 50 mL.

Infusion with IV Bag

• Prepare an IV bag of 0.9% sodium chloride with volume equal to the total infusion volume minus the volume of reconstituted remdesivir solution that will be diluted to achieve a 1.25 mg/mL solution.
• Withdraw the required volume of reconstituted solution containing remdesivir for injection into an appropriately sized syringe.
• Transfer the required volume of reconstituted remdesivir for injection to the 0.9% sodium chloride infusion bag.
• Gently invert the bag 20 times to mix the solution in the bag. Do not shake.

Infusion with Syringe

• Select an appropriately sized syringe equal to or larger than the calculated total infusion volume of 1.25 mg/mL remdesivir solution needed.
• Withdraw the required volume of 100 mg/20 mL (5 mg/mL) reconstituted remdesivir solution from the vial into the syringe followed by the required volume of 0.9% sodium chloride needed to achieve a 1.25 mg/mL remdesivir solution.
• Mix the syringe by inversion 20 times.
• The prepared diluted solution is stable for 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 24 hours in the refrigerator at 2°C to 8°C (36°F to 46°F) (including any time before dilution into intravenous infusion fluids).

Reference:

1. FDA Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Veklury (remdesivir). Available at: https://www.fda.gov/media/137566/download. Accessed August 5, 2020.