HAWAIʻI PACIFIC HEALTH | KAPIʻOLANI PALI MOMI STRAUB WILCOX

CREATING A HEALTHIER HAWAIʻI

FDA Emergency Use Authorization of Remdesivir

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Remdesivir (RDV) has been issued an Emergency Use Authorization (EUA) by the FDA for the treatment of COVID-19. RDV is an investigational drug that has not been approved by the FDA for any use. It is not yet known if RDV is safe and effective for the treatment of COVID-19.

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	The optimal dosing and duration of treatment is unknown. The suggested dosing below may be updated as more data emerges. <u>Adult and peds pts ≥40kg NOT requiring mechanical ventilation and/or ECMO:</u> 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>Adult and peds pts ≥40kg requiring mechanical ventilation and/or ECMO:</u> 200mg IV on Day 1, then 100mg IV q24h on Days 2-10 <u>Peds pts 3.5-<40kg NOT requiring mechanical ventilation and/or ECMO:</u> 5mg/kg IV on Day 1, then 2.5mg/kg IV q24h on Days 2-5. If patient does not demonstrate clinical improvement, may extend treatment up to a total of 10 days. <u>Peds pts 3.5-<40kg requiring mechanical ventilation and/or ECMO:</u> 5mg/kg IV on Day 1, then 2.5mg/kg 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. Pediatric Use: 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. Infusion-related reactions have been reported with administration of RDV. If s/sx of a clinically significant infusion reaction occur, immediately discontinue administration of RDV 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	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, 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.
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)."

Reference:

1. FDA Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Remdesivir (GS-5734). Available at: https://www.fda.gov/media/137566/download. Accessed May 5, 2020.

Appendix A. 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, 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).

Appendix B. Administration and Preparation of Remdesivir (RDV) for Pediatric Patients <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.

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 18 solution. It is always recommended to administer IV medication immediately after preparation when possible.

• Using Table 5 and Table 6, determine the volume of 0.9% saline to withdraw from the infusion bag. Table 5 and Table 6 include the volume requirements for preparing pediatric weight-based dosing regimens at 5 mg/kg and 2.5 mg/kg, respectively.

Table 5. Recommended Remdesivir Loading Dose Dilution Instructions for Pediatric Patients Weighing 3.5 kg to <40kg.

Weight (kg)	Pediatric loading dose for weight <40kg; 5mg/kg (mg)	NS bag size	Volume of NS to be withdrawn and discarded from NS bag (ml)	Required volume of reconstituted remdesivir for injection (ml)
3.5	17.5	25ml	3.5	3.5
4	20		4	4
5	25		5	5
7.5	37.5	50ml	7.5	7.5
10	50		10	10
15	75	100ml	15	15
20	100		20	20
25	125		25	25
30	150		30	30
35	175	250ml	35	35

Table 6. Recommended Remdesivir Maintenance Dose Dilution Instructions for Pediatric Patients Weighing 3.5 kg to <40kg.

Weight (kg)	Pediatric maintenance dose for weight <40kg; 2.5mg/kg (mg)	NS bag size	Volume of NS to be withdrawn and discarded from NS bag (ml)	Required volume of reconstituted remdesivir for injection (ml)
3.5	8.8	25ml	0	1.8
4	10		0	2
5	12.5		2.5	2.5
7.5	18.8	50ml	3.8	3.8
10	25		5	5
15	37.5		7.5	7.5
20	50		10	10
25	62.5	100ml	12.5	12.5
30	75		15	15
35	87.5		17.5	17.5

• 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 5 or 6. 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) (including any time before dilution into intravenous infusion fluids).