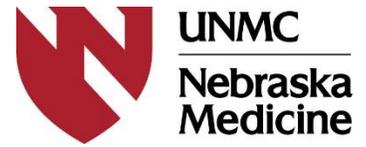


Remdesivir Use for COVID-19 at Nebraska Medicine

(Updated 11/2/2020)



Remdesivir is a nucleoside analogue that interferes with RNA polymerase, effectively terminating replication of SARS-CoV-2. There are currently two different pathways for remdesivir treatment at Nebraska Medicine; an ongoing clinical trial, or an FDA-approved supply (under an Emergency Use Authorization for pediatrics). Clinical trial enrollment remains the preferred option for patients with moderate to severe COVID-19 disease, wherever possible. The COVID ID physician may be able to assist with determining the most appropriate option for your patient.

Clinical Trial Enrollment: The NIH/NIAID clinical trial ACTT-3 is two-armed and is investigating remdesivir vs. remdesivir + interferon beta-1a for patients with these entry criteria:

- **Inclusion Criteria:** Age ≥ 18 ; PCR confirmed SARS-CoV-2 infection within past 3 days OR within the past 7 days and progressive COVID-19 disease; one of: 1) infiltrates on chest imaging 2) requiring supplemental oxygen 3) $S_pO_2 \leq 94\%$ on RA
- **Exclusion Criteria:** AST or ALT $> 5x$ ULN; eGFR < 30 or on dialysis; WBC $< 1.5k$; platelets $< 50k$; on or being prepared for ECMO therapy; pregnancy or breast feeding; anticipated discharge within 3 days; history of chronic liver disease; receipt of > 2 doses of remdesivir prior to enrollment; receipt of convalescent plasma or IVIG for COVID-19; receipt of any interferon product in past 2 weeks; receipt of tyrosine kinase inhibitors, TNF inhibitors, interleukin inhibitors, or T- and B-cell monoclonal antibodies in past 2 weeks

Contact Dr. Andre Kalil (402-888-2953) and/or LuAnn Larson (402-321-0775) to initiate the trial enrollment process.

FDA-approved Supply: Remdesivir has now been FDA-approved for treatment of COVID-19 in adults and pediatrics ≥ 12 years old and $\geq 40kg$. Those who do not meet these criteria may still receive remdesivir under the restrictions of the FDA Emergency Use Authorization (EUA).

Nebraska Medicine Selection Criteria - Consider these additional selection criteria to promote optimal use of remdesivir in all patients given current clinical trial data:

- Recommendation for 5 days of total therapy (may consider shorter/longer according to clinical status)
- Recommendation for patients with $S_pO_2 \leq 94\%$ on RA or requiring supplemental oxygen
- Recommendation for patients clinically worsening, but not yet requiring mechanical ventilation or mechanically ventilated for $< 24hrs$ (initiation as early as possible in the clinical course preferred)
- Recommendation for use in patients with reasonable functional status expected after discharge

Dosing - The dosing regimen for adults and children $> 40kg$ is: remdesivir 200mg IV once, then 100mg IV daily

- There is an order panel to ease the EPIC ordering process following discussion with the COVID ID physician (take care not to enter the remdesivir orders with an IRB# intended for the NIH study). Patients who rapidly recover and are discharged before receiving the 5-day treatment course will complete therapy early. Remdesivir should not be given in an infusion center and the patient should not remain hospitalized solely to complete therapy.

Remdesivir EUA Use for Pediatrics

EUA Patient Selection Criteria

- Age <12 years old and 3.5-40kg with inpatient admission status
- PCR confirmed SARS-CoV-2 infection
- Expected to require hospitalization for more than 72hrs (therapy may only be given as an inpatient)
- Confirmed AST/ALT <10x ULN

Pediatric dosing (3.5 - 40 kg): 5 mg/kg IV once, then 2.5 mg/kg IV daily. Lyophilized powder formulation only.

These logistical requirements are required for providers using remdesivir **only** for patients meeting the EUA criteria to maintain regulatory compliance. They must be completed prior to order entry to avoid a hard stop:

- Providers **must discuss** the unapproved status of this medication, risks/benefits of remdesivir therapy, and information on any possible alternatives to receiving therapy with the patient/family/PoA, and provide them with the “Fact Sheet for Parents and Caregivers” (can be found at <https://www.gilead.com/remdesivir>)
 - This discussion should provide clear information to the patient/caregiver and allow them to ask any questions they may have, but does not require signed informed consent. Providing the Fact Sheet can be deferred due to the emergent nature of treatment, but that discussion must be documented prior to ordering the medication.
 - **Prior to order entry**, providers must document discussion of treatment in the medical record using the dot phrase “.remdesiviremergencyuse” and complete the smart fields. It may be helpful to file a note solely for the purpose of this documentation to avoid a hard stop upon order entry. This will satisfy FDA documentation requirements.
- Providers **must report all adverse events** potentially attributable to remdesivir through our SOS system. Adverse events will be reviewed and an FDA MedWatch report and notification to Gilead completed on your behalf as required by EUA.
 - The EUA defines an adverse event as, “death; a life-threatening adverse event; prolongation of an inpatient hospitalization; a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; a congenital anomaly; need for a medical/surgical intervention to prevent death.” Thus, negative events for a patient on remdesivir should be reported even if they are only potentially related to the medication.
- Daily laboratory monitoring requirement: CBC and CMP

General Remdesivir Warnings, Precautions, and Adverse Effects

- Infusion-related reactions (IRRs)
 - Signs and symptoms of IRRs include: hypotension, nausea, vomiting, diaphoresis, shivering.
 - Nebraska Medicine dilutes remdesivir in 250 mL of normal saline and administers the drug over 60 minutes to minimize these adverse effects, but the drug may be concentrated in 100 mL for patients that are fluid restricted. Infusion length can vary from 30 to 120 minutes.
- Elevated transaminase levels (alanine aminotransferase – ALT)
 - ALT elevations can occur
 - In patients with ALT equal to or greater than 10x ULN, remdesivir therapy shouldn’t be started.
 - In patients with a rise in ALT ≥10x ULN during treatment, remdesivir should be held.

- In patients with an ALT elevation in conjunction with s/s of liver inflammation or an increase in conjugated bilirubin or alkaline phosphatase or INR, remdesivir should be discontinued.
- Renal dysfunction
 - Remdesivir and its active metabolite [are renally eliminated](#) and there is no data evaluating these entities in severe renal impairment, although accumulation over the short duration of therapy for COVID-19 is not anticipated to be clinically significant.
 - The package insert and EUA state that remdesivir is “not recommended” in those with an eGFR <30mL/min due to potential build-up of the carrier molecule cyclodextrin (SBECD). This issue has been thoroughly investigated with the IV formulation of voriconazole, which contains very similar quantities of cyclodextrin to remdesivir. Multiple retrospective studies have not demonstrated a nephrotoxic effect of cyclodextrin with the use of IV voriconazole in patients with CrCL<30.
 - We recommend that remdesivir be administered to adults without regard to the patient’s renal function
- Hydroxychloroquine/chloroquine drug interaction
 - *In vitro* antagonism has been proposed demonstrating lower remdesivir antiviral activity in patients on concomitant hydroxychloroquine/chloroquine. The package insert states that coadministration is not recommended. Consider risk/benefit ratio or discuss with rheumatology the feasibility of discontinuation of hydroxychloroquine/chloroquine during remdesivir use.
- In the [ACTT-1 clinical trial](#), patients with severe COVID-19 were treated with either remdesivir or placebo. Both groups demonstrated equivalent rates of all adverse events grade 3 or above (29% vs 33%, respectively) as well as transaminase elevations specifically (0.6% vs 1.1%, respectively).
- [In the SIMPLE trial](#), patients with severe COVID-19 were treated with remdesivir for 5 or 10 days. Both groups had >70% of the population experience an adverse event while clinical improvement was similar in both arms.

Group	5 day (n=200)	10 day (n=197)
All AEs	71%	74%
Serious AE	21%	35%
Grade ≥3 AE	31%	43%
Discontinued treatment d/t AE	5%	10%
All-cause mortality (Day 28)	10%	13%

- In a different [randomized, placebo-controlled trial of remdesivir](#) from China in which approximately one-third of patients received lopinavir/ritonavir and interferon alfa-2b plus two-thirds received corticosteroids:

Adverse Effects, n (%)	Remdesivir (n=155)	Placebo (n=79)
Any	102 (66%)	50 (64%)
AST elevation	7 (5)	9 (12)
Thrombocytopenia	16 (10)	5 (6)
Rash	11 (7)	5 (6)
Constipation	21 (14)	12 (15)
Serious	28 (18)	20 (26)
Acute Kidney Injury	1 (1)	0 (0)
Requiring Discontinuation	18 (12)	4 (5)
ALT elevation	2 (1)	0 (0)
ARDS/respiratory failure	7 (5)	1 (1)