

New Mexico Medical Advisory Team (MAT) Assessment Remdesivir Treatment Guidelines

MAT Workgroup: Clinical Care

Updated: July 27, 2020

Question/Request:

1. How should remdesivir be distributed within a hospital facility?
2. Which patients should be prioritized for treatment with remdesivir?

Recommendations:

New Mexico will not receive enough remdesivir for hospitals to allow every eligible patient to be treated with remdesivir under the Emergency Use Authorization.¹ We recommend allocating remdesivir to hospital facilities and patients based on the guidelines provided by the National Institutes of Health on July 24, 2020 “NIH COVID-19 Treatment Guidelines” (<https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/remdesivir/>). This clinical framework is intended to provide clear parameters for the selection of patients who will receive treatment with remdesivir and reduce any potential for bias due to race, ethnicity, gender, disabilities, do not resuscitate/do not intubate (DNR/DNI) status, socio economic status, rural residency, age, education status or occupation. Treating individual patients remains a physician and evidence-based process.

Recommendation for Prioritizing Limited Supplies of Remdesivir

- **Because remdesivir supplies are limited, we agree with the NIH guidelines and recommend that remdesivir be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). In this section, “high-flow oxygen” refers to the receipt of supplemental oxygen through a high-flow device.**

Recommendation for Patients with Mild or Moderate COVID-19

- There are insufficient data to recommend either for or against the use of remdesivir in patients with mild or moderate COVID-19.

Recommendation for Patients with COVID-19 Who Are on Supplemental Oxygen but Who Do Not Require High-Flow Oxygen, Noninvasive or Invasive Mechanical Ventilation, or ECMO

- **We recommend using remdesivir for 5 days or until hospital discharge, whichever comes first.**
- If a patient who is on supplemental oxygen while receiving remdesivir progresses to requiring high-flow oxygen, noninvasive or invasive mechanical ventilation, or ECMO, the course of remdesivir should be completed.

Recommendation for Patients with COVID-19 Who Require High-Flow Oxygen, Noninvasive Ventilation, Mechanical Ventilation, or ECMO

- Because there is uncertainty regarding whether starting remdesivir confers clinical benefit in these groups of patients, the NIH guidelines do not make a recommendation either for or against starting remdesivir.

Duration of Therapy for Patients Who Have Not Shown Clinical Improvement After 5 Days of Therapy

- **There are insufficient data on the optimal duration of remdesivir therapy for patients with COVID-19 who have not shown clinical improvement after 5 days of therapy.** Some experts extend the total remdesivir treatment duration to up to 10 days.

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Assessment and Considerations:

These criteria are based on evidence from randomized trials of remdesivir. In a preliminary report of a randomized, placebo-controlled trial, remdesivir reduced time to recovery in COVID-19 positive patients.² **The patients with the clearest evidence of clinical benefit from remdesivir were those who required supplemental oxygen but who did not require high-flow oxygen, noninvasive or mechanical ventilation, or ECMO at baseline (n = 421). In this subgroup, those who received remdesivir had a shorter time to recovery (recovery rate ratio 1.47; 95% confidence interval [CI], 1.17–1.84); in a post-hoc analysis of deaths by Day 14, remdesivir appeared to confer a survival benefit (hazard ratio [HR] for death 0.22; 95% CI, 0.08–0.58).** Finally, in a large, multinational, randomized open-label trial in hospitalized patients with severe COVID-19, **remdesivir treatment for 5 or 10 days had similar clinical benefit.**³

Dosing Information⁴

- The suggested dose for adults and pediatric patients weighing ≥ 40 kg is a single dose of 200 mg infused intravenously over 30 to 120 minutes on Day 1 followed by once-daily maintenance doses of 100 mg infused intravenously over 30 to 120 minutes for 4 days (days 2 through 5). If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e., up to a total of 10 days).
- The suggested dose for pediatric patients with body weight between 3.5 kg and <40 kg is a single loading dose of remdesivir 5 mg/kg IV (infused over 30 to 120 min) on Day 1 followed by remdesivir 2.5 mg/kg IV (infused over 30 to 120 min) once daily for 4 days (days 2 through 5). If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e., up to a total of 10 days).

Monitoring, Adverse Effects, and Drug-Drug Interactions (from NIH guidelines)

- Remdesivir can cause gastrointestinal symptoms (e.g., nausea, vomiting), elevated transaminase levels, and an increase in prothrombin time (without a change in the international normalized ratio).
- Clinical drug-drug interaction studies of remdesivir have not been conducted. Remdesivir levels are unlikely to be substantially altered by cytochrome P450 (CYP) 2C8, CYP2D6, or CYP3A4 enzymes, or by P-glycoprotein (P-gp) or organic anion-transporting polypeptide (OATP) drug transporters. Remdesivir may be administered with weak to moderate inducers or with strong inhibitors of CYP450, OATP, or P-gp. Strong induction may modestly reduce remdesivir levels. The clinical relevance of lower remdesivir levels is unknown. Based on information provided by Gilead (written communication, July 2020), the use of remdesivir with strong inducers (e.g., rifampin) is not recommended.
- Minimal to no reduction in remdesivir exposure is expected when remdesivir is coadministered with dexamethasone, according to information provided by Gilead (written communication, July 2020).
- Chloroquine or hydroxychloroquine may decrease the antiviral activity of remdesivir; coadministration of these drugs is not recommended.⁵
- Because the remdesivir formulation contains renally cleared sulfobutylether-beta-cyclodextrin sodium, patients with an eGFR of <50 mL/min are excluded from some clinical trials (some trials have an eGFR cutoff of <30 mL/min).

Considerations in Pregnancy (from NIH guidelines)

- Use remdesivir in pregnant patients only when the potential benefit justifies the potential risk to the mother and the fetus.⁴

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- The safety and effectiveness of remdesivir for treatment of COVID-19 have not been evaluated in pregnant patients. Remdesivir should not be withheld from pregnant patients if it is otherwise indicated. Remdesivir is available through the Food and Drug Administration (FDA) Emergency Use Authorization (EUA) for adults and children and through compassionate use programs for pregnant women and children with COVID-19.
- Ninety-eight female participants received remdesivir as part of a randomized controlled trial for the treatment of Ebola virus infection; six of these participants had a positive pregnancy test. The obstetric and neonatal outcomes were not reported in the study.⁶

Considerations in Children (from NIH guidelines)

- The safety and effectiveness of remdesivir for treatment of COVID-19 have not been evaluated in pediatric patients.
- Remdesivir is available through an FDA EUA for adults and children and through compassionate use programs for children with COVID-19.
- A clinical trial is currently evaluating the pharmacokinetics of remdesivir in children (ClinicalTrials.gov identifier [NCT04431453](https://clinicaltrials.gov/ct2/show/study/NCT04431453)). In the same randomized controlled trial for the treatment of Ebola virus infection discussed above, 41 pediatric patients received remdesivir.⁶ These patients included neonates and children aged <18 years.¹⁰ The safety and clinical outcomes for children were not reported separately in the published results for the trial.

Red flags and concerns:

Administration of remdesivir requires adherence to strict reporting guidelines set by the FDA, which include:

1. Documenting in the patient's medical record that the patient/caregiver has been:
 - a. Given the fact sheet for patients and parents/caregivers
 - b. Informed of alternatives for receiving remdesivir, and
 - c. Informed that remdesivir is an unapproved drug that is authorized for use under EUA
 - d. Consented to receiving treatment
2. Adult and pediatric patients must have an eGFR and full-term neonates must have serum creatinine determined prior to remdesivir first administration. All adult patients must have creatinine clearance determined before dosing.
3. Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir.

Additionally, the prescribing health care provider is responsible for mandatory reporting of all medication errors and adverse events considered to be potentially related to remdesivir within 7 calendar days of the event. These additional reporting requirements may be challenging for smaller facilities who are less accustomed to clinical trials and other requirements associated with the administration of medications under emergency use authorizations. The DOH should coordinate with these smaller facilities and provide support for tracking required data parameters, where appropriate.

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Resources/Reference:

1. Federal Drug Administration Remdesivir EUA Authorization Letter
<https://www.fda.gov/media/137564/download>
2. Beigel, J. H., Tomashek, K. M., Dodd, L. E., Mehta, A. K., Zingman, B. S., Kalil, A. C., ... & Lopez de Castilla, D. (2020). Remdesivir for the Treatment of Covid-19—Preliminary Report. *New England Journal of Medicine*. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32445440>.
3. Goldman, J., Lye, D., Hui, D., ...Sen Gupta, D. (2020) Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *New England Journal of Medicine* DOI: 10.1056/NEJMoa2015301 Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32459919>.
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