Indian Health Service
National Pharmacy and Therapeutics Committee

COVID-19 Emerging Treatments Update

Original May 5, 2020 (Updated August 31, 2020)

Remdesivir (Veklury®)
-EMERGENCY USE AUTHORIZATION-

Mechanism of Action[1,2]: Broad spectrum antiviral; inhibits RNA synthesis. Remdesivir demonstrates evidence of in vitro activity against SARS-CoV-2 and in vivo in animal models. Early exploratory analysis suggested remdesivir may improve outcomes for patients admitted to the hospital with severe disease.

Current Status[3]: Remdesivir is not FDA approved. On May 1, 2020, the FDA issued an Emergency Use Authorization (EUA) for remdesivir use in hospitalized adult and pediatric patients with severe COVID-19, defined as oxygen saturation ≤ 94% on room air, or requiring supplemental oxygen or mechanical ventilation or extracorporeal membrane oxygenation (ECMO). ***On August 28, 2020, the FDA updated the remdesivir EUA and expanded its use to include treatment of all hospitalized adult and pediatric patients with suspected or laboratory-confirmed COVID-19, regardless of disease severity.***

Availability[3-5]: Distribution of remdesivir under the EUA was initially controlled by the U.S. government for use consistent with terms and conditions of the EUA. The manufacturer supplied remdesivir to authorized distributors, or directly to a U.S. government agency, who distributed the drug to hospitals and other healthcare facilities as directed by the U.S. government, in collaboration with state and local government authorities, as needed. Remdesivir is now available for purchase through the pharmaceutical vendor, AmerisourceBergen.

Efficacy[6-9]: To date, four studies of significance have reported clinical outcomes with remdesivir use; all studies have been published in peer-reviewed journals. These studies are succinctly detailed below.

Compassionate use of remdesivir for patients with severe COVID-19 – *published April 10, 2020*

Design:	International, multi-center cohort study in nine countries including the U.S.
Patients:	53 adults hospitalized with severe COVID-19 received 10 days of remdesivir
1° Outcome:	68% of patients (36/53) showed improvement in oxygen-support class
Limitation(s):	Small sample size, no placebo comparator, no data reported on viral load changes

Remdesivir in adults with severe COVID-19 – *published April 29, 2020*

Design:	Randomized, double-blinded, placebo-controlled trial at 10 hospitals in Hubei, China
Patients:	158 adults hospitalized for COVID-19 with pneumonia received 10 days of remdesivir
1° Outcome:	No difference in time to clinical improvement (HR 1.23; 95% CI: 0.87-1.75)
Limitation(s)	Enrollment stopped due to lack of available patients; insufficiently powered to detect outcome

Adaptive COVID-19 treatment trial (ACTT) – *published May 22, 2020*

Design:	Phase 3 adaptive, randomized, double-blinded, placebo-controlled trial launched in the U.S.
Patients:	1063 adults hospitalized with advanced COVID-19 and lung involvement (preliminary data only)
1° Outcome:	Time to recovery was reported as 31% faster for remdesivir patients (11 vs. 15 days, p<0.001)
Limitation(s):	Preliminary findings only

Remdesivir for 5 or 10 days in patients with severe COVID-19 (SIMPLE Trial) – *published May 27, 2020*

Design:	Phase 3 multi-site, international, randomized, open-label trial in 15 countries including the U.S.
Patients:	397 adults hospitalized for COVID-19 with pneumonia received either 5- or 10-day durations
1° Outcome:	No difference in improvement on Day 14 between remdesivir durations (60% vs. 52%, p=0.014)
Limitation(s):	Unknown study patient demographics, no placebo comparator

Recommended Dosing[3]: Dosing guidance provided in the EUA recommends the following:

- *Adults and pediatric patients (>40 kg): 200 mg IV on day 1, then 100 mg IV daily for 5 or 10 days*
- *Pediatrics patients (3.5 kg - 40 kg): 5 mg/kg/dose on day 1, then 2.5 mg/kg/dose daily for 5 or 10 days*

Duration of therapy is determined by the need for mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO). In patients receiving mechanical ventilation and/or ECMO, 10 days of remdesivir are recommended. Patients not mechanically ventilated &/or provided ECMO should receive 5 days of remdesivir.

Warnings/Cautions[3]: Not recommended if eGFR ≤ 30ml/min (or receiving dialysis), or if ALT is >5 times ULN. Hepatic lab testing should be performed before and daily during treatment. Caution in kidney impairment due to the possible accumulation of drug excipients. Remdesivir should be discontinued immediately if clinically significant infusion-related reactions occur (i.e., hypotension, nausea, vomiting, diaphoresis).

Remdesivir is supplied in 100 mg vials for reconstitution and does not contain preservatives or a bacteriostatic agent. Any unused portion of a single-dose vial should be discarded after a dilated solution is prepared. Administer IV medication immediately after preparation when possible.

Patient Monitoring: The EUA recommends the following laboratories be performed prior to starting remdesivir and daily on all patients while receiving remdesivir:

- Hepatic testing
- Renal function tests (serum creatinine and eGFR)

Adverse Drug Events[7,8] (ADE): In an early analysis, approximately 70% of patients taking remdesivir experienced any ADE. Two percent of ADEs were considered serious and medication discontinuation resulting from ADEs occurred in 5-10% of remdesivir patients. In the only published randomized trial with a placebo comparator, the rates of overall and serious adverse events were similar between groups. Medication discontinuations due to adverse events were numerically higher in remdesivir patients (12% vs 5%).

Per the EUA, all medication errors and serious / unexpected ADEs must be reported to the FDA MedWatch program within 7 calendar days. Additional guidance is provided below:

- *should include the words "Remdesivir under Emergency Use Authorization" in the description*
- *should include the words "Indian Health Service" in the description or the reporter section (section G)*
- Information on the FDA MedWatch program can be found on the IHS Pharmacovigilance website

Patient/Family/Caregiver Information: Mandatory requirements from the EUA for remdesivir patients or family members are available by accessing the following link: https://www.fda.gov/media/137565/download. Suggested IHS patient education codes for documentation include:

- **U07.01 – M** to indicate education regarding pharmacologic treatment for COVID-19
- **U07.01 – L** when providing literature (handouts) related to the pharmacologic treatment for COVID-19

References:

1. Infectious Diseases Society of America. Guidelines on the Treatment and Management of Patients with COVID-19.
2. European Medicines Agency. Summary on compassionate use: Remdesivir Gilead. April 3, 2020.
3. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers. Emergency Use Authorization of Remdesivir. (Veklury).
4. American Society of Health Systems Pharmacists. Assessment of Evidence for COVID-19-Related Treatments (Evidence Table)
5. Working to Supply Remdesivir for COVID-19. © 2020 Gilead Sciences, Inc. All rights reserved.
6. Grein J, Ohmagari N, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. NEJM 2020. DOI: 10.1056/NEJMoa2007016
7. Wang Y, Zhang D, et al. Remdesivir in adults with severe COVID-19. Lancet 2020, doi.org/10.1016/S0140-6736(20)31022-9.
8. Beigel JH, Tomashek KM, et al. Remdesivir for the treatment of COVID-19 – Preliminary Report. NEJM. 2020. DOI: 10.1056/NEJMoa2007764
9. Goldman JD, Lye DC, et al. Remdesivir for 5 or 10 days in patients with severe COVID-19. NEJM. 2020. DOI: 10.1056/NEJMoa2015301