DRAFT Guidance to Iowa Hospitals on the Use of Remdesivir in Treatment of Patients with COVID-19

Background

On May 1, 2020, the U.S. Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for the investigational antiviral drug Remdesivir (Gilead) for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease (ABC; FDA). This approval was based on a National Institute of Allergy and Infectious Diseases (NIAID) sponsored adaptive, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of novel therapeutic agents in hospitalized adults diagnosed with COVID-19. The trial was limited to adults but the EUA allows for treatment of children (age not specified) (ClinicalTrials.gov).

"The preliminary data showed that the time to recovery was 11 days on Remdesivir compared to 15 days for placebo, a 31% decrease. The mortality rate for the Remdesivir group was 8%, compared to 11.6% for the placebo group; that mortality difference was not statistically significant" (STAT News).

Distribution to states

Following issuance of the EUA, Gilead donated 607,000 doses of Remdesivir to the U.S. government for distribution to hospitals for the treatment of in-patients with a diagnosis of severe COVID-19 disease. The Office of the Assistant Secretary for Preparedness and Response (ASPR) in the Department of Health and Human Services was tasked to distribute the drug to hospitals in states over a 6-week period. On May 5, the Office notified states, including Iowa, to receive the initial distribution of Remdesivir. ASPR has not stated its specific criteria for allocation to states but has stated that its assessment will be based on ethical (equity) and clinical principles (Dr. John Redd, telephone call, May 5th.)

On May 5, IDPH informed ASPR that it had decided to centrally receive all future shipments of Remdesivir to the State for re-distribution to hospitals, as determined by IDPH. The first shipment to Iowa included 10 cases, each case containing 40 doses of the drug. The second shipment to Iowa included 34 cases also containing 40 doses of the drug. The shipped formulation requires cold chain management throughout the distribution process. The size and frequency of subsequent weekly shipments is currently unknown. The product is scarce and the number of eligible patients based on EUA criteria alone may outpace the supply, so ethical principles, data, and clinical judgments will inform the distribution of Remdesivir to facilities, and the allocation of Remdesivir to eligible patients within facilities.

Remdesivir Advisory Committee

On June 2, and again on June 19, an advisory committee to the Iowa Department of Public Health, the Remdesivir Advisory Committee (RAC), convened to respond to and further develop

guidance for use of Remdesivir in hospitalized patients. The members of the RAC included hospital representatives and physicians led by the IDPH Director, Gerd Clabaugh. The charge to the RAC was to develop statewide guidance for the use of Remdesivir in hospitalized patients, taking into consideration the exclusion and inclusion criteria of the NIAID clinical trial, the specifics of the EUA, the EUA provider fact sheet and any available protocols established by hospitals participating in any of the Gilead Remdesivir clinical trials. The RAC guidance, when endorsed by IDPH, should inform usage, but is not a substitute for individualized clinical decision-making by treating physicians following hospital policies for use of restricted drugs.

FDA Provider Factsheet

> The product must only be administered to eligible patients, as defined in the FDA Provider Fact Sheet: "Treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in adults and children hospitalized with severe disease. Severe disease is defined as patients with an oxygen saturation (SpO2) ≤ 94% on room air **or** requiring supplemental oxygen **or** requiring invasive mechanical ventilation **or** requiring ECMO. Specifically, Remdesivir 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."

Recommendations

1. The RAC recommends that patients (children and adults) receive only a 5-day course of treatment, beginning as early in the disease course as possible (e.g. ≤ 10 days of symptoms), preferably before a patient requires mechanical ventilation.
2. The EUA permits the use of Remdesivir in pregnant women but "… should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus". (FDA Provider Fact Sheet)
3. Treating physicians should adhere to the requirements of the EUA and to their hospital guidelines and policies in using restricted drugs.
4. The RAC recommends that Remdesivir be used in eligible patients on a first-come, first-served basis.
5. Access to Remdesivir will be limited to those hospitals with intensive care unit capability.

Inclusion Criteria:

1. All ages are eligible for use of Remdesivir.
2. Patients must be hospitalized with symptoms suggestive of COVID-19 infection.

3. Generalized hospital consent to treatment is sufficient for the use of Remdesivir under the EUA.
4. The patient should have suspected or laboratory-confirmed SARS-CoV-2 infection.
5. The patient may have illness of any duration, and at least one of the following:
- Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR
- SpO2 < / = 94% on room air, OR
- Requiring supplemental oxygen, OR
- Requiring mechanical ventilation.

Exclusion Criteria:

1. Any patient previously receiving Remdesivir in a clinical trial or in the expanded access (compassionate use) program.

2. Alanine Transaminase (ALT) or Aspartate Transaminase (AST) > 5 times the upper limit of normal.

3. Estimated glomerular filtration rate (eGFR) < 30 ml/min (including patients receiving hemodialysis or hemofiltration).

4. Anticipated discharge from the hospital within 72 hours.

5. Allergy to Remdesivir

Specific Formula for re-distribution to Iowa Hospitals from the State of Iowa:

1. The current allocation formula is based upon the following data submitted by Iowa hospitals daily to IDPH:
   a. Total number of COVID-19 positive inpatients reported daily
   b. Total number of COVID-19 positive patients on ventilator reported daily.
2. These numbers are averaged and added across the previous 7 day period
3. Total average numbers of 1a and 1b were summed for each hospital ("Raw Score")
4. A total allocation score was derived as each hospital's individual portion of the score as a part of the overall total of scores
5. Distribution occurs in case allotments to eliminate the need of breaking down cases and thereby ease repackaging and distribution of the product.

$$\frac{Total\ number\ of\ COVID\ inpatients}{7\ days} + \frac{Total\ number\ of\ COVID\ vent\ patients}{7\ days} = raw\ score$$

$$\frac{Individual\ raw\ score}{Sum\ of\ all\ raw\ scores} = Allocation\ Score$$

6. Evaluate location and quantities of current supply prior to distribution of subsequent shipments to ensure reasonable equity of supply across Iowa.