Penn Medicine Remdesivir Emergency Use Authorization Guidelines for Use  
Last Updated: May 15, 2020  
For updated criteria visit www.uphs.upenn.edu/antibiotics/COVID19.html

General Principles:

• In the short term, because there will be extremely limited supply of Emergency Use Authorization (EUA) remdesivir, it will be allocated through a randomization process (see Appendix 1) after a “Request for Allocation of EUA Remdesivir” is made by the primary physician or team treating the patient (see appropriate section below on how to make this request) as long as the patient meets eligibility criteria below at the time of referral

• Available supply will be allocated to eligible patients without holding supply for future patients

• If a patient is initiated on remdesivir, then a complete course of 5 or 10 days depending on severity of illness at initiation (see below) will be reserved for that patient until the patient has completed the recommended duration or the patient stops therapy prematurely, which most commonly will occur if the patient is discharged or is otherwise doing sufficiently well, the patient dies, or the patient has experienced an adverse event that requires discontinuation of remdesivir

• Patients at hospitals that have access to clinical trials should preferentially be evaluated for these trials to determine eligibility and willingness to participate, but trial eligibility should not preclude eligibility for EUA remdesivir
  o To evaluate a patient for eligibility and enrollment in a clinical trial at the Hospital of the University of Pennsylvania (HUP) or Penn Presbyterian Medical Center (PPMC), send a Cureatr message to the pool “Remdesivir and Convalescent Plasma Clinical Trials”
  o For more information on EUA remdesivir in the context of clinical trials, see “Clinical Trials” section below

• Remdesivir should not be used outside of the acute hospital setting, even in patients that received it as an inpatient and are discharged; patients who are discharged while still within the treatment duration window will be considered to have completed treatment

• For more information, refer to Food and Drug Administration (FDA) (https://www.fda.gov/media/137566/download) “Fact Sheet for Healthcare Providers”

Request for Allocation of EUA Remdesivir:

• Chester County Hospital (CCH), Lancaster General Hospital (LGH), Penn Medicine Princeton Medical Center (PMPMC) and Pennsylvania Hospital (PAH): EUA for remdesivir is available only through infectious diseases consultation. Infectious diseases consultants will communicate requests for remdesivir to the antibiotic stewardship program personnel to evaluate for allocation based on drug availability and patient eligibility according to the inclusion and exclusion criteria below. Consultation of infectious diseases for remdesivir does not constitute approval for remdesivir so should not be framed to patients as such. Allocation depends on supply and patient eligibility.

• Hospital of the University of Pennsylvania (HUP) and Penn Presbyterian Medical Center (PPMC): For specific criteria during designated hours, refer to Table 1 below:

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Table 1. Procedure for requesting remdesivir EUA allocation at HUP and PPMC.*

<table>
<thead>
<tr>
<th>Day and Time</th>
<th>HUP Procedure</th>
<th>PPMC Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekdays 8a-5p</td>
<td>Contact the antibiotic stewardship team through the ILÚM app or web-based software and request remdesivir similar to other restricted antibiotics (for instructions on use of ILÚM go to the following link: <a href="http://www.uphs.upenn.edu/antibiotics/antibiotic_approval/index.html">http://www.uphs.upenn.edu/antibiotics/antibiotic_approval/index.html</a>. Initial triage for remdesivir allocation will be performed by the antibiotic stewardship team. If patients are able to receive an allocation of remdesivir, the antibiotic stewardship team will contact the treating team and trigger an official infectious diseases consultation as a condition to receive EUA remdesivir.</td>
<td></td>
</tr>
<tr>
<td>Weekends and Holidays 8a-5p</td>
<td>Contact the antibiotic stewardship team through ILÚM as above, and the process will work as described on weekdays.</td>
<td>Contact the antibiotic stewardship team through ILÚM AND request an official infectious diseases consultation. These groups will discuss and determine the potential allocation of remdesivir.</td>
</tr>
<tr>
<td>Sunday 5p-8a, Monday 5p-8a, Tuesday 5p-8a, Wednesday 5p-8a, Thursday 5p-8a</td>
<td>Contact the antibiotic stewardship team through ILÚM as above. The request will be in the queue for review when the antibiotic stewardship is available at 8a the following morning. Receipt of remdesivir is not an emergency so it will not be administered as a stat dose overnight. Initial triage for remdesivir allocation will be performed by the antibiotic stewardship team. If patients are able to receive an allocation of remdesivir, the antibiotic stewardship team will contact the treating team and trigger an official infectious diseases consultation as a condition to receive EUA remdesivir.</td>
<td></td>
</tr>
<tr>
<td>Friday 5p-8a, Saturday 5p-8a, Night before holiday 5p-8a</td>
<td>Contact the antibiotic stewardship team through ILÚM as per weekday and non-holiday evenings as above, and the process will work as described on these days.</td>
<td>Contact the antibiotic stewardship team through ILÚM at any time AND request an official infectious diseases consultation after 8a the following morning, and the process will work as described on weekend and holiday days.</td>
</tr>
</tbody>
</table>

*A request for remdesivir submitted through these channels at HUP and PPMC does not constitute approval for remdesivir so should not be framed to patients as such. Allocation depends on supply and patient eligibility as determined by infectious diseases consultation. For any questions or concerns, contact Keith Hamilton (HUP) or Naasha Talati (PPMC).

- All hospitals will track patients who have been referred for EUA remdesivir including those patients who receive remdesivir and those that do not as well as reasons why they did not.

**Inclusion Criteria for Receipt of EUA Remdesivir**
- Should be used ONLY in patients with laboratory confirmed SARS-CoV-2 infection by RT-PCR that was performed ≤96 hours prior to initiation of EUA remdesivir
- Should be considered in hospitalized patients with creatinine clearance >30 mL/min who have severe disease, defined as SpO2 ≤94% on room air or requiring supplemental oxygen or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) AND bilateral pulmonary infiltrates on chest radiograph (chest X-ray or CT scan)

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Exclusion Criteria for EUA Remdesivir

- Should not be initiated in pregnant patients; these patients should have remdesivir obtained through the Gilead compassionate use protocol: [https://rdvcu.gilead.com/](https://rdvcu.gilead.com/)
- Should not be initiated in patients with mild-moderate disease, defined as SpO2 >94% not requiring supplemental oxygenation or ventilation
- Should not be initiated in patients with creatinine clearance <30 and/or receiving hemodialysis or other forms of renal replacement therapy because its use in this population and appropriate dosing has not been well defined. If creatinine drops <30 while receiving remdesivir risks and benefits to continuing the medication should be weighed
- Should not be initiated in patients with allergy to remdesivir or components
- Should not be initiated in patients with ALT ≥5 times upper limit of normal at baseline
- Should not be initiated in patients who have been on ventilator or ECMO for ≥5 days
- Should not be initiated in patients who have previously received remdesivir for SARS-CoV-2 through EUA or another mechanism such as a research trial
- Should not be used in patients who are terminally ill from a non-COVID-19 underlying disease with life expectancy less than 6 months
- Should not be used in patients in ongoing clinical trials or Expanded Access protocols unless other specified in section on “Clinical Trials”

Clinical Trials:

- EUA remdesivir will not be allocated to patients in ongoing clinical trials unless remdesivir is explicitly permitted by the protocol; if a protocol calls for participants to receive remdesivir as an affirmative part of the trial design, sponsors must secure access through means other than EUA
- Patients who decline participation in or withdraw from clinical trials will be eligible for EUA remdesivir allocation, assuming other criteria are satisfied; however, patients must withdraw prior to consideration
- Expanded Access (e.g. convalescent plasma via Cleveland Clinic Expanded Access Protocol) is not considered a clinical trial; patients who are currently receiving an investigational product through Expanded Access will not be allocated EUA remdesivir during active Expanded Access use
- Patients who previously received other investigational products for the treatment of COVID-19, whether through clinical trial, Expanded Access, or other avenue, will be eligible for EUA remdesivir allocation, assuming other criteria are satisfied
- See Appendix 2 for more details and rationale on EUA remdesivir and clinical trials

Statement of Non-Discrimination: Allocation for EUA remdesivir will NOT consider or be based on any of the following:

- Race or ethnicity
- Gender, gender identity, or sexual orientation
- Citizenship, immigration status, or socioeconomic status
- Religion
- Socioeconomic factors, health insurance, or lack of health insurance
- Age as a criterion alone
- Disability or comorbid condition(s) as criteria alone
- Judgments about potential quality of life
- Judgments about perceived importance of individual patients

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Treatment Course:
- All treatment courses should be stopped at discharge (patients cannot receive remdesivir at home)
- Length of acute care hospital stay should not be extended for the sole purpose of receiving the full treatment course of remdesivir; patients should be discharged when they are otherwise medically appropriate for discharge as determined by their primary treatment team
- Otherwise, target duration should be determined using the following criteria:
  - 10 days duration is recommended for patients requiring invasive mechanical ventilation and/or ECMO at initiation of remdesivir, but there should be reassessment at 5 days to determine important factors such as clinical trajectory/improvement and goals of care to determine if the medication should be continued beyond 5 days
  - 5 days duration is recommended for patients not requiring invasive mechanical ventilation and/or ECMO at initiation of remdesivir

Dosing:
- 200 mg x 1 loading dose (day 1)
- 100 mg daily maintenance dose starting on day 2

Monitoring:
- All patients should have creatinine checked prior to and monitored daily during treatment
- All patients should have liver function tests checked prior to and monitored daily during treatment
- All women of child-bearing potential should have a pregnancy checked within 2 days prior to initiation of remdesivir

Discontinuation:
- Patients who develop ALT values ≥5 times upper limit of normal during treatment (can be restarted when it drops <5 times upper limit of normal based on weighing the risks and benefits of restarting the medication)
- Patients who develop ALT elevation above the upper limit of normal accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR

Patient and/or Family Discussion: The consulting infectious diseases physician(s) should communicate the following with patients and/or families once the patient has been determined to receive allocation of the drug and not before. They should be provided "Fact Sheet for Patients and Parents/Caregivers" (https://www.fda.gov/media/137565/download):
  - FDA has authorized the emergency use of remdesivir, which is not an FDA approved drug
  - The patient or parent or legally authorized representative has the option to accept or refuse remdesivir
  - The significant known and potential risks and benefits of remdesivir, and the extent to which such risks and benefits are unknown
  - Information on available alternative treatments and the risks and benefits of those alternatives
  - If providing this information will delay the administration of remdesivir to a degree that would endanger the lives of patients, the information must be provided to the patients as soon as possible after remdesivir is administered

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Appendix 1. Randomization process for allocation of remdesivir.

- Each Penn Medicine hospital will review requests for remdesivir on an ongoing basis throughout business hours (8a-5p) after receiving a request according to the procedures described in the section "Request for Allocation of EUA Remdesivir." Receipt of remdesivir is not an emergency so doses will not be dispensed during hours outside those listed above.

- Each hospital will determine the frequency of review based on patient volume and drug availability.

- No antibiotic stewardship personnel actively involved in the clinical care of COVID-19 patients (i.e. acting as an infectious diseases consultant) will be able to run the randomization process and should make sure another member of the team or a qualified proxy runs the randomization process.

- If there is enough EUA remdesivir available at a hospital to accommodate all the patients in a typical review period, then all eligible patients will be allocated EUA remdesivir.

- If there is not enough EUA remdesivir available at a hospital to accommodate all the patients in a typical review period, then a randomization process will be employed on eligible patients with eligibility criteria described previously in order to determine which patients will receive remdesivir; a suggested approach to the randomization process is as follows:
  - Export relevant patients from the secure EUA remdesivir database to Excel on a secure hospital-issued device.
  - Insert a column before all of the patient information labeled “Randomization Number.”
  - Block the first column to include all of the patient rows as shown:

![Excel screenshot showing randomization process](image)

  - Then type =RAND():

![Excel screenshot showing RAND function](image)
o Then press CTRL + Enter, which will generate random numbers from 0 to 1

![Excel spreadsheet showing randomization numbers](Image)

o Patients will then be contacted for receipt of remdesivir **in order from lowest number (closest to 0) to highest (closest to 1)** until the remdesivir courses are exhausted (either 5-day or 10-day courses should be reserved based on criteria outlined in the section “Treatment Course”). In this example, patient 3 would be contacted first, followed by patients 1, 2, 5, and 4 until EUA remdesivir courses are exhausted. To make the order easier to review, the rows could be **sorted by the “Randomization Number” column from lowest to highest** after running the randomization.

o Patient(s) who not qualify in a particular round of randomization will be included in subsequent rounds of randomization if drug becomes available again along as the patient still fits eligibility criteria as described previously.
Appendix 2. Rationale for guidelines on EUA in the context of enrollment in clinical trials.

**General principle:** All patients who could benefit should be eligible to receive EUA remdesivir outside of clinical trials.

**Question 1:** Should EUA remdesivir be allocated to patients in ongoing trials?

**Answer 1:** No.

For trials in which all participants are not already receiving remdesivir, sponsors, investigators, and Institutional Review Boards should consider whether the baseline standard of care for all participants should be altered to include remdesivir. However, drug will not be allocated from EUA supply for this purpose. There is insufficient remdesivir to provide doses to all clinical trial participants, and providing it only to a subset would negatively impact the integrity of study data. Given existing scarcity, it is ethically acceptable not to alter the trial standard of care at this time. Drug needed to change trial standard of care must be secured by trial sponsors separate from the EUA allocation. [See also Q3 below.]

**Question 2:** Should patients who are eligible for ongoing trials, including those studying remdesivir or other drugs for treatment of COVID-19, but who decline to participate be eligible for EUA allocation of remdesivir?

**Answer 2:** Yes.

Before there is evidence of a drug’s safety and effectiveness, it is reasonable to make access contingent on participation in clinical trials for which a patient is eligible, whether for the drug of interest or other drugs being studied for the same indication. This prioritizes the ability to gather crucial data through clinical trials and does not withhold anything of proven value from patients. It is for this reason that Expanded Access is limited to patients unable to participate in clinical trials of the requested drug.

However, once there is evidence of proven value for a given product, as there now is for remdesivir sufficient to support the EUA (and likely traditional marketing approval), patients facing serious/life threatening disease have a strong interest in securing access. This is why standards of care change for ongoing and newly initiated trials as new information becomes available (although it may not always be possible to do this for reasons of scarcity). Importantly, this does not mean that patients are necessarily entitled to access and it may be impossible to provide it to all patients given limited supply. But each patient who could benefit from the product should have the opportunity to be considered for allocation, regardless of whether they are eligible to participate in a trial of that drug or another for the same indication. This is because there is more certainty about benefit from the drug than would be available from clinical trial participation, which may entail receipt of other unproven interventions with different risk profiles, and, in some cases, may include randomization to placebo.

Nonetheless, clinical trial participation is preferred and should be both offered and encouraged, as there may be other important questions to resolve about the drug of interest (i.e., mortality benefit from remdesivir), as well as about other drugs under study for the indication that may ultimately be demonstrated superior to the requested product. Participation should not be required in order to be eligible for receipt of a drug under EUA, however.

There is a possibility that this approach will discourage participation in important clinical trials. However, given current scarcity of remdesivir, the impact on trials should be minimal. Once scarcity...
improves, it is likely that trial standards of care will change as well, such that there will be no incentive to avoid participation in order to secure remdesivir.

**Question 3:** Should patients who withdraw from a COVID-19 drug trial be eligible for EUA allocation of remdesivir?

**Answer 3:** Yes.

For the same reasons described above regarding greater certainty of benefit, patients who drop out of ongoing COVID-19 drug trials should be eligible to be considered for allocation of EUA remdesivir. However, they must withdraw from the trial in order to be considered, rather than waiting to see whether their request for remdesivir is granted before deciding to do so. This will help encourage continued trial participation as appropriate, with flexibility for participants to decide to pursue another alternative.

**Question 4:** Should patients who have received other investigational products and fared poorly be eligible for EUA allocation of remdesivir?

**Answer 4:** Yes.

Patients who have fared poorly on other interventions should be eligible for consideration to receive EUA remdesivir, so long as they are not enrolled in an ongoing trial. Having a prior opportunity to try an investigational product should not preclude the opportunity to be considered for access to a product with proven benefit.