FACT SHEET FOR HEALTH CARE PROVIDERS
EMERGENCY USE AUTHORIZATION (EUA) OF REMDESIVIR (GS-5734™)

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product remdesivir for treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in adults and pediatric patients 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 mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).

This EUA is for the use of remdesivir to treat COVID-19.
Remdesivir must be administered by intravenous (IV) infusion.

Health care providers must submit a report on all medication errors and **ALL SERIOUS ADVERSE EVENTS** related to remdesivir. See Sections 8 and 9 of the Full EUA Prescribing Information for reporting requirements.

- See the Full EUA Prescribing Information for complete dosage, administration, and preparation instructions.
- Remdesivir is available as a lyophilized powder and concentrated solution.
- The recommended dose for adults and pediatric patients weighing 40 kg and higher is a single loading dose of 200 mg on Day 1 followed by once-daily maintenance doses of 100 mg from Day 2.
- **For pediatric patients weighing 3.5 kg to less than 40 kg, only use remdesivir for injection, 100 mg, lyophilized powder.** The recommended dose for pediatric patients weighing 3.5 kg to less than 40 kg is a single loading dose of remdesivir 5 mg/kg on Day 1 followed by remdesivir 2.5 mg/kg once daily from Day 2 (see Full EUA Prescribing Information, subsection 2.3 Recommended Dosage in Pediatric Patients).
- The optimal duration of treatment for COVID-19 is unknown.
- For patients requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO), the recommended total treatment duration is 10 days.
- For patients not requiring invasive mechanical ventilation and/or ECMO, the recommended total treatment duration is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days for a total treatment duration of up to 10 days.
- Administer remdesivir via IV infusion over 30 to 120 minutes.

For information on clinical trials that are testing the use of remdesivir in COVID-19, please see www.clinicaltrials.gov.

INSTRUCTIONS FOR ADMINISTRATION

This section provides essential information on the unapproved use of remdesivir, an unapproved drug, to treat suspected or laboratory confirmed COVID-19 in adults and pediatric patients hospitalized with severe disease under this EUA. **For more information, see the long version of the "Fact Sheet for Health Care Providers," available at https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.**

Contraindications

Remdesivir is contraindicated in patients with known hypersensitivity to any ingredient of remdesivir.

Dosing

Patient Selection and Treatment Initiation

- Empiric treatment of hospitalized patients with suspected COVID-19 can be considered pending laboratory confirmation of SARS-CoV-2 infection.
- Remdesivir can be used at any time after onset of symptoms in hospitalized patients.
- Adult and pediatric patients greater than 28 days old) must have an estimated glomerular filtration rate (eGFR) determined and full-term neonates (at least 7 days to less than or equal to 28 days old) must have serum creatinine determined before dosing and daily while receiving remdesivir.
- Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir.

Adult Patients

- The recommended dosage of remdesivir for adults is a single loading dose of 200 mg on Day 1 followed by once-daily maintenance doses of 100 mg from Day 2.
- For patients requiring invasive mechanical ventilation and/or ECMO, the recommended total treatment duration is 10 days.
- For patients not requiring invasive mechanical ventilation and/or ECMO, the recommended total treatment duration is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days for a total treatment duration of up to 10 days.
- Administer remdesivir via IV infusion over 30 to 120 minutes.

Pediatric Patients

- **For pediatric patients weighing 3.5 kg to less than 40 kg, use remdesivir for injection, 100 mg, lyophilized powder only.** Remdesivir

injection, 100 mg/20 mL (5 mg/mL), should not be used for pediatric patients weighing 3.5 kg to less than 40 kg due to the higher amount of sulfobutylether-β-cyclodextrin sodium salt [SBECD] present and resulting higher tonicity of the solution concentrate compared to the lyophilized formulation. Administer a body weight-based dosing regimen of a single loading dose of remdesivir 5 mg/kg on Day 1 followed by remdesivir 2.5 mg/kg once daily from Day 2 (see Full EUA Prescribing Information, subsection 2.3 Recommended Dosage in Pediatric Patients).

- The recommended dosage of remdesivir for pediatric patients weighing 40 kg and higher is the adult dosage regimen of a single loading dose of 200 mg on Day 1 followed by once-daily maintenance doses of 100 mg from Day 2 (see Full EUA Prescribing Information, subsection 2.3 Recommended Dosage in Pediatric Patients). Table 1 below provides the recommended dosage and dosage form in pediatric patients.

Table 1: Recommended Dosage Form and Dosage in Pediatric Patients

Body weight	Recommended dosage form	Loading dose (on Day 1)	Maintenance dose (from Day 2)
3.5 kg to less than 40 kg	**Remdesivir Lyophilized Powder for Injection Only**	5 mg/kg	2.5 mg/kg
40 kg and higher	Remdesivir Lyophilized Powder for Injection or Remdesivir Injection	200 mg	100 mg

- For patients requiring invasive mechanical ventilation and/or ECMO, total treatment duration is 10 days.
- For patients not requiring invasive mechanical ventilation and/or ECMO, total treatment duration is 5 days. 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).
- Administer remdesivir via IV infusion over 30 to 120 minutes (see Full EUA Prescribing Information, subsection 2.3 Recommended Dosage in Pediatric Patients).

Pregnancy

Remdesivir should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus.

Renal Impairment

Patients with eGFR greater than or equal to 30 mL/min have received remdesivir for treatment of COVID-19 with no dose adjustment. The safety and efficacy of remdesivir have not been assessed in patients with severe renal impairment or ESRD. Remdesivir is not recommended in adult and pediatric patients (greater than 28 days old) with eGFR less than 30 mL/min or in full-term neonates (at

least 7 days to less than or equal to 28 days old) with serum creatinine greater than or equal to 1 mg/dL unless the potential benefit outweighs the potential risk.

Adult and pediatric patients (greater than 28 days old) must have an eGFR determined and full-term neonates (at least 7 days to less than or equal to 28 days old) must have serum creatinine determined before dosing and daily while receiving remdesivir.

Adults

- eGFR, Male: (140 – age in years) × (weight in kg) / 72 × (serum creatinine in mg/dL);
- eGFR, Female: (140 – age in years) × (weight in kg) × 0.85 / 72 × (serum creatinine in mg/dL)

Pediatric patients (greater than 28 days old to less than 1 year of age)

- eGFR: 0.45 × (height in cm) / serum creatinine in mg/dL

Pediatric patients (at least 1 year of age to less than 18 years of age)

- eGFR =
  0.413 x (height or length)/Scr) if height/length is expressed in centimeters
  OR
  41.3 x (height or length)/Scr) if height/length is expressed in meters

Hepatic Impairment

It is not known if dosage adjustment is needed in patients with hepatic impairment, and remdesivir should only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk.

Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir.

Dose Preparation

Care should be taken during admixture to prevent inadvertent microbial contamination. As there is no preservative or bacteriostatic agent present in this product, aseptic technique must be used in preparation of the final parenteral solution. It is always recommended to administer IV medication immediately after preparation when possible.

Store diluted remdesivir solution for infusion up to 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

Important Preparation and Administration Instructions

- There are important differences in the preparation of the lyophilized powder and the concentrated solution. Refer to the complete preparation,

storage, and administration instructions in the Full EUA Prescribing Information, subsections 2.7 and 2.8.

- **Remdesivir for Injection, 100 mg:** Reconstitute remdesivir for injection lyophilized powder with 19 mL of Sterile Water for Injection and further dilute in 0.9% sodium chloride infusion bag prior to administration.
- **Remdesivir Injection, 100 mg/20 mL (5 mg/mL):** Dilute remdesivir injection concentrated solution in 0.9% sodium chloride infusion bag prior to administration.
- Prepare solution for infusion on same day as administration.
- Administer diluted remdesivir as an IV infusion over 30 to 120 minutes.
- After infusion is complete, flush with 0.9% sodium chloride.
- Discard any remaining reconstituted remdesivir lyophilized powder, reconcentrated solution, and diluted solution.

Storage and Handling of Prepared Dosages

IMPORTANT:
This product contains no preservative. Any unused portion of a single-dose remdesivir vial should be discarded after a diluted solution is prepared.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Should either be observed, the solution should be discarded and fresh solution prepared.

The prepared diluted solution should not be administered simultaneously with any other medication. The compatibility of remdesivir injection with IV solutions and medications other than 0.9% sodium chloride is not known.

Warnings

There are limited clinical data available for remdesivir. Serious and unexpected adverse events may occur that have not been previously reported with remdesivir use.

Hypersensitivity Including Infusion-Related and Anaphylactic Reactions

Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed during and following administration of remdesivir. Signs and symptoms may include hypotension, tachycardia, bradycardia, dyspnea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of remdesivir and initiate appropriate treatment. The

use of remdesivir is contraindicated in patients with known hypersensitivity to remdesivir *[see Full EUA Prescribing Information, Contraindications (4)].*

Increased Risk of Transaminase Elevations

Transaminase elevations have been observed in healthy volunteers who received 200 mg of remdesivir followed by 100 mg doses for 5 to10 days. Transaminase elevations have also been reported in patients with COVID-19 who received remdesivir in clinical trials. As transaminase elevations have been reported as a component of COVID-19, including in patients receiving placebo in clinical trials of remdesivir, discerning the contribution of remdesivir to transaminase elevations in this patient population is challenging.

Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir.

- Remdesivir should not be initiated in patients with ALT greater than or equal to 5 times the upper limit of normal (ULN) at baseline.
- Remdesivir should be discontinued in patients who develop:
    - ALT greater than or equal to 5 times the ULN during treatment with remdesivir. Remdesivir may be restarted when ALT is less than 5 times the ULN.
      OR
    - ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.

Risk of Reduced Antiviral Activity When Coadministered with Chloroquine or Hydroxychloroquine

Coadministration of remdesivir and chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on in vitro data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of remdesivir *[see Full EUA Prescribing Information, Drug interactions (10), Microbiology/resistance information (15)].*

Serious Side Effects

An adverse reaction associated with remdesivir in clinical trials in healthy adult subjects was increased liver transaminases. Additional adverse reactions associated with the drug, some of which may be serious, may become apparent with more widespread use.

INSTRUCTIONS FOR HEALTH CARE PROVIDERS

As the health care provider, you must communicate to your patient or parent/caregiver information consistent with the "Fact Sheet for Patients and Parents/Caregivers" (and provide a copy of the Fact Sheet) prior to the patient receiving remdesivir, including:

- FDA has authorized the emergency use of remdesivir, which is not an FDA approved drug.
- The patient or parent/caregiver 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 practicable after remdesivir is administered.

For information on clinical trials that are testing the use of remdesivir for COVID-19, please see www.clinicaltrials.gov.

MANDATORY REQUIREMENTS FOR REMDESIVIR ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION:

In order to mitigate the risks of using this unapproved product under EUA and to optimize the potential benefit of remdesivir, the following items are required. Use of unapproved remdesivir under this EUA is limited to the following (all requirements **must** be met):

1. Treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in adults and pediatric patients 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.
2. As the health care provider, communicate to your patient or parent/caregiver information consistent with the "Fact Sheet for Patients and Parents/Caregivers" prior to the patient receiving remdesivir. Health

care providers (to the extent practicable given the circumstances of the emergency) must document 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 to receiving remdesivir, and
    c. Informed that remdesivir is an unapproved drug that is authorized for use under EUA.
3. Adult and pediatric patients (greater than 28 days old) must have an eGFR determined and full-term neonates (at least 7 days to less than or equal to 28 days old) must have serum creatinine determined prior to remdesivir first administration and daily while receiving remdesivir.
4. Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir.
5. Patients with known hypersensitivity to any ingredient of remdesivir must not receive remdesivir.
6. The prescribing health care provider and/or the provider's designee are/is responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of remdesivir.
7. The prescribing health care provider and/or the provider's designee are/is responsible for mandatory reporting of all medication errors and adverse events (death, serious adverse events*) considered to be potentially related to remdesivir occurring during remdesivir treatment within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "Remdesivir under Emergency Use Authorization (EUA)" in the description section of the report.

    - Submit adverse event reports to FDA MedWatch using one of the following methods:
        - Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
        - By using a postage-paid Form FDA 3500 (available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf) and returning by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787), or by fax (1-800-FDA-0178), or
        - Call 1-800-FDA-1088 to request a reporting form
        - Submitted reports should include in the field name, "Describe Event, Problem, or Product Use/Medication Error" a statement **"Remdesivir under Emergency Use Authorization (EUA)."**

*Serious Adverse Events are defined as:

- death;
- a life-threatening adverse event;
- inpatient hospitalization or prolongation of existing hospitalization;

- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect;
- a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

[see Adverse Reactions and Medication Errors Reporting Requirements and Instructions (8)]

OTHER REPORTING REQUIREMENTS
In addition please provide a copy of all FDA MedWatch forms to:
Gilead Pharmacovigilance and Epidemiology
Fax: 1-650-522-5477
E-mail: Safety_fc@gilead.com

APPROVED AVAILABLE ALTERNATIVES

There is no approved available alternative product. There are EUAs for other COVID-19 treatments. Additional information on COVID-19 treatments can be found at https://www.cdc.gov/coronavirus/2019-ncov/index.html. The health care provider should visit https://clinicaltrials.gov/ to determine whether the patient may be eligible for enrollment in a clinical trial.

AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of HHS has declared a public health emergency that justifies the emergency use of remdesivir to treat COVID-19 caused by SARS-CoV-2. In response, the FDA has issued an EUA for the unapproved product, remdesivir, for the treatment of COVID-19.[1] As a health care provider, you must comply with the mandatory requirements of the EUA (see below).

FDA issued this EUA, requested by Gilead Sciences, Inc. and based on their submitted data.

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that remdesivir may be effective for the treatment of COVID-19 in patients as specified in this Fact Sheet. You may be contacted and asked to provide information to help with the assessment of the use of the product during this emergency.

This EUA for remdesivir will end when the Secretary determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA is no longer needed.

[1] The health care provider should visit clinicaltrials.gov to determine whether there is an active clinical trial for the product in this disease/condition and whether enrollment of the patient(s) in a clinical trial is more appropriate than product use under this EUA.

FULL EUA PRESCRIBING INFORMATION

FULL EUA PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

1. AUTHORIZED USE

Remdesivir is authorized for use under an EUA for treatment of patients hospitalized with suspected or laboratory confirmed SARS-CoV-2 infection and severe disease. Severe disease is defined as patients with an oxygen saturation (SpO2) ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO). Specifically, remdesivir is only authorized for hospitalized adult and pediatric patients for whom use of an intravenous (IV) agent is clinically appropriate.

2. DOSAGE AND ADMINISTRATION

2.1 Important Testing Prior to and During Treatment and Route of Administration

- Adult and pediatric patients (greater than 28 days old) must have an eGFR determined and full-term neonates (at least 7 days to less than or equal to 28 days old) must have serum creatinine determined before dosing of remdesivir and daily while receiving remdesivir *[see Dosage and Administration (2.5), Use in Specific Populations (11.5)]*.
- Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir *[see Dosage and*

Administration (2.6), Warnings and Precautions (5.2), Use in Specific Populations (11.6)].

- Remdesivir should be administered via IV infusion only. Do not administer as an intramuscular (IM) injection.

2.2 Recommended Dosage in Adult Patients

- The recommended dosage in adults is a single loading dose of remdesivir 200 mg on Day 1 followed by once-daily maintenance doses of remdesivir 100 mg from Day 2 via IV infusion.
- For patients requiring invasive mechanical ventilation and/or ECMO, total treatment duration is 10 days.
- For patients not requiring invasive mechanical ventilation and/or ECMO, total treatment duration is 5 days. 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).
- Administer remdesivir via IV infusion in a total volume of up to 250 mL 0.9% sodium chloride over 30 to 120 minutes *[see Dosage and Administration (2.7)]*.

2.3 Recommended Dosage in Pediatric Patients

For pediatric patients weighing 3.5 kg to less than 40 kg, the dose should be calculated using the mg/kg dose according to the patient's weight *[see Dosage and Administration (2.8), Use in Specific Populations (11.3)]:*

- **For pediatric patients weighing 3.5 kg to less than 40 kg, use remdesivir for injection, 100 mg, lyophilized powder only**. Do not use remdesivir injection, 100 mg/20 mL (5 mg/mL), for pediatric patients weighing 3.5 kg to less than 40 kg due to the higher amount of SBECD present and resulting higher tonicity of the solution concentrate compared to the lyophilized formulation.
- Refer to Table 1 below for recommended dosage form and dosage in pediatric patients according to weight.

Table 1: Recommended Dosage Form and Dosage in Pediatric Patients

Body weight	**Recommended dosage form**	**Loading dose (on Day 1)**	**Maintenance dose (from Day 2)**
3.5 kg to less than 40 kg	**Remdesivir Lyophilized Powder for Injection Only**	5 mg/kg	2.5 mg/kg
40 kg and higher	Remdesivir Lyophilized Powder for Injection or Remdesivir Injection	200 mg	100 mg

- For pediatric patients requiring invasive mechanical ventilation and/or ECMO, total treatment duration is 10 days.
- For pediatric patients not requiring invasive mechanical ventilation and/or ECMO, total treatment duration Is 5 days. 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).

2.4 Pregnancy

Remdesivir should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus.

2.5 Renal Impairment

Adult and pediatric patients (greater than 28 days old) must have an eGFR determined and full-term neonates (at least 7 days to less than or equal to 28 days old) must have serum creatinine determined before dosing and daily while receiving remdesivir *[see Use in Specific Populations (11.5)]*.

Adults

- eGFR, Male: (140 – age in years) × (weight in kg) / 72 × (serum creatinine in mg/dL);
- eGFR, Female: (140 – age in years) × (weight in kg) × 0.85 / 72 × (serum creatinine in mg/dL)

Pediatric patients (greater than 28 days old to less than 1 year of age)

- eGFR: 0.45 × (height in cm) / serum creatinine in mg/dL

Pediatric patients (at least 1 year of age to less than 18 years of age)

- eGFR =
  0.413 x (height or length)/Scr) if height/length is expressed in centimeters
  OR
  41.3 x (height or length)/Scr) if height/length is expressed in meters

Because the excipient SBECD is renally cleared and accumulates in patients with decreased renal function, administration of drugs formulated with SBECD [such as remdesivir is not recommended in adults and pediatric patients (greater than 28 days old) with eGFR less than 30 mL/min or in full-term neonates (at least 7 days and less than or equal to 28 days old)] with serum creatinine greater than or equal to 1 mg/dL unless the potential benefit outweighs the potential risk.

2.6 Hepatic Impairment

It is not known if dosage adjustment is needed in patients with hepatic impairment, and remdesivir should only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk *[see Warnings and Precautions (5.2), Use in Specific Populations (11.6)].*

Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir.

2.7 Dose Preparation and Administration, Adults and Pediatric Patients Weighing 40 kg and Higher

Adults and pediatric patients weighing 40 kg and higher can use remdesivir for injection, 100 mg, lyophilized powder and remdesivir injection, 100 mg/20 mL (5 mg/mL), solution. See below for different preparation and administration instructions for the two dosage formulations.

Remdesivir for Injection, 100 mg, Lyophilized Powder

Reconstitution Instructions

Remove the required number of single-dose vial(s) from storage. For each vial:

- Aseptically reconstitute remdesivir lyophilized powder by addition of 19 mL of Sterile Water for Injection using a suitably sized syringe and needle per vial.
- Discard the vial if a vacuum does not pull the Sterile Water for Injection into the vial.
- Immediately shake the vial for 30 seconds.
- Allow the contents of the vial to settle for 2 to 3 minutes. A clear solution should result.
- If the contents of the vial are not completely dissolved, shake the vial again for 30 seconds and allow the contents to settle for 2 to 3 minutes. Repeat this procedure as necessary until the contents of the vial are completely dissolved.
- Following reconstitution, each vial contains 100 mg/20 mL (5 mg/mL) of remdesivir solution.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
- After reconstitution, the total storage time before administration should not exceed 4 hours at room temperature or 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

Dilution Instructions

Care should be taken during admixture to prevent inadvertent microbial contamination. As there is no preservative or bacteriostatic agent present in this product, aseptic technique must be used in preparation of the final parenteral solution. It is always recommended to administer IV medication immediately after preparation when possible.

- The reconstituted remdesivir lyophilized powder for injection, containing 100 mg/20 mL remdesivir solution, should be further diluted in 100 mL or 250 mL 0.9% sodium chloride infusion bags.
- Using Table 2, determine the volume of 0.9% sodium chloride to withdraw from the infusion bag.

Table 2: Recommended Dilution Instructions Using Reconstituted Remdesivir for Injection Lyophilized Powder in Adults and Pediatric Patients Weighing 40 kg and Higher

Remdesivir dose	0.9% sodium chloride infusion bag volume to be used	Volume to be withdrawn and discarded from 0.9% sodium chloride infusion bag	Required volume of reconstituted remdesivir for injection
200 mg (2 vials)	250 mL	40 mL	40 mL (2 × 20 mL)
	100 mL	40 mL	40 mL (2 × 20 mL)
100 mg (1 vial)	250 mL	20 mL	20 mL
	100 mL	20 mL	20 mL

- Withdraw and discard the required volume of 0.9% sodium chloride from the bag per Table 2 using an appropriately sized syringe and needle.
- Withdraw the required volume of reconstituted remdesivir for injection from the remdesivir vial using an appropriately sized syringe per Table 2. Discard any unused portion remaining in the remdesivir vial.
- Transfer the required volume of reconstituted remdesivir for injection to the selected infusion bag.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- The prepared diluted solution is stable for 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 24 hours in the refrigerator at 2°C to 8°C (36°F to 46°F).

Administration Instructions

The prepared diluted solution should not be administered simultaneously with any other IV medication. The compatibility of remdesivir injection with IV solutions and medications other than 0.9% sodium chloride is not known.

Administer the diluted solution with the infusion rate described in Table 3.

Table 3: Recommended Rate of Infusion — Diluted Remdesivir for Injection Lyophilized Powder in Adults and Pediatric Patients Weighing 40 kg and Higher

Infusion bag volume	Infusion time	Rate of infusion
250 mL	30 min	8.33 mL/min
	60 min	4.17 mL/min
	120 min	2.08 mL/min
100 mL	30 min	3.33 mL/min
	60 min	1.67 mL/min
	120 min	0.83 mL/min

Remdesivir Injection, 100 mg/20 mL (5 mg/mL), Solution

Dilution Instructions

Care should be taken during admixture to prevent inadvertent microbial contamination. As there is no preservative or bacteriostatic agent present in this product, aseptic technique must be used in preparation of the final parenteral solution. It is always recommended to administer IV medication immediately after preparation when possible.

- Remove the required number of single-dose vial(s) from storage. Each vial contains 100 mg of remdesivir. For each vial:
    - Equilibrate to room temperature (20°C to 25°C [68°F to 77°F]). Sealed vials can be stored up to 12 hours at room temperature prior to dilution.
    - Inspect the vial to ensure the container closure is free from defects and the solution is free of particulate matter.
- Using Table 4, determine the volume of 0.9% sodium chloride to withdraw from the infusion bag.

Table 4: Recommended Dilution Instructions— Remdesivir Solution in Adults and Pediatric Patients Weighing 40 kg and Higher

Remdesivir dose	0.9% sodium chloride infusion bag volume to be used	Volume to be withdrawn and discarded from 0.9% sodium chloride infusion bag	Required volume of remdesivir injection solution
200 mg (2 vials)	250 mL	40 mL	40 mL (2 × 20 mL)
100 mg (1 vial)		20 mL	20 mL

- Withdraw and discard the required volume of 0.9% sodium chloride from the bag per Table 4 using an appropriately sized syringe and needle.
- Withdraw the required volume of remdesivir injection solution from the remdesivir vial using an appropriately sized syringe per Table 4.
    - Pull the syringe plunger rod back to fill the syringe with approximately 10 mL of air.
    - Inject the air into the remdesivir injection vial above the level of the solution.
    - Invert the vial and withdraw the required volume of remdesivir injection solution into the syringe. The last 5 mL of solution requires more force to withdraw.
- Discard any unused solution remaining in the remdesivir vial.
- Transfer the required volume of remdesivir injection solution to the infusion bag.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- The prepared diluted solution is stable for 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 24 hours in the refrigerator at 2°C to 8°C (36°F to 46°F).

Administration Instructions

The prepared diluted solution should not be administered simultaneously with any other medication. The compatibility of remdesivir injection with IV solutions and medications other than 0.9% sodium chloride is not known.

Administer the diluted solution with the infusion rate described in Table 5.

Table 5: Recommended Rate of Infusion—Diluted Remdesivir Solution in Adults and Pediatric Patients Weighing 40 kg and Higher

Infusion bag volume	Infusion time	Rate of infusion
250 mL	30 min	8.33 mL/min
	60 min	4.17 mL/min
	120 min	2.08 mL/min

2.8 Dose Preparation and Administration, Pediatric Patients Weighing 3.5 kg to Less Than 40 kg

For pediatric patients weighing 3.5 kg to less than 40 kg, use remdesivir for injection, 100 mg, lyophilized powder only. Remdesivir injection, 100 mg/20 mL (5 mg/mL), should not be used for pediatric patients weighing 3.5 kg to less than 40 kg due to the higher amount of SBECD present and resulting higher tonicity of the solution concentrate compared to the lyophilized formulation.

Remdesivir for Injection, 100 mg, Lyophilized Powder

Reconstitution Instructions

Remove the required number of single-dose vial(s) from storage. For each vial:

- Aseptically reconstitute remdesivir lyophilized powder by addition of 19 mL of Sterile Water for Injection using a suitably sized syringe and needle per vial.
    - Discard the vial if a vacuum does not pull the Sterile Water for Injection into the vial.
- Immediately shake the vial for 30 seconds.
- Allow the contents of the vial to settle for 2 to 3 minutes. A clear solution should result.
- If the contents of the vial are not completely dissolved, shake the vial again for 30 seconds and allow the contents to settle for 2 to 3 minutes. Repeat this procedure as necessary until the contents of the vial are completely dissolved.
- Following reconstitution, each vial contains 100 mg/20 mL (5 mg/mL) of remdesivir solution.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
- After reconstitution, the total storage time before administration should not exceed 4 hours at room temperature or 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

Dilution Instructions

- **Care should be taken during admixture to prevent inadvertent microbial contamination.** As there is no preservative or bacteriostatic agent present in this product, aseptic technique must be used in preparation of the final parenteral solution. It is always recommended to administer IV medication immediately after preparation when possible. Following reconstitution as instructed above, each vial will contain a 100 mg/20 mL (5 mg/mL) remdesivir concentrated solution. For pediatric patients weighing 3.5 kg to less than 40 kg, the 100 mg/20 mL (5 mg/mL) remdesivir concentrate should be further diluted to a fixed concentration of 1.25 mg/mL using 0.9% sodium chloride.
- The total required infusion volume of the 1.25 mg/mL remdesivir solution for infusion is calculated from the pediatric weight-based dosing regimens of 5 mg/kg for the Loading Dose and 2.5 mg/kg for each Maintenance Dose.
- Small 0.9% sodium chloride infusion bags (e.g., 25, 50, or 100 mL) or an appropriately sized syringe should be used for pediatric dosing. The recommended dose is administered via IV infusion in a total volume dependent on the dose to yield the target remdesivir concentration of 1.25 mg/mL.
- A syringe may be used for delivering volumes less than 50 mL.

Infusion with IV Bag

- Prepare an IV bag of 0.9% sodium chloride with volume equal to the total infusion volume minus the volume of reconstituted remdesivir solution that will be diluted to achieve a 1.25 mg/mL solution.
- Withdraw the required volume of reconstituted solution containing remdesivir for injection into an appropriately sized syringe.
- Transfer the required volume of reconstituted remdesivir for injection to the 0.9% sodium chloride infusion bag.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.

Infusion with Syringe

- Select an appropriately sized syringe equal to or larger than the calculated total infusion volume of 1.25 mg/mL remdesivir solution needed.
- Withdraw the required volume of 100 mg/20 mL (5 mg/mL) reconstituted remdesivir solution from the vial into the syringe followed by the required volume of 0.9% sodium chloride needed to achieve a 1.25 mg/mL remdesivir solution.
- Mix the syringe by inversion 20 times.
- The prepared diluted solution is stable for 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 24 hours in the refrigerator at 2°C to 8°C (36°F to 46°F) (including any time before dilution into intravenous infusion fluids).

Administration Instructions
The prepared diluted solution should not be administered simultaneously with any other medication. The compatibility of remdesivir injection with IV solutions and medications other than 0.9% sodium chloride is not known.

Administer the diluted solution with the infusion rate described in Table 6.

Table 6: Recommended Rate of Infusion—Diluted Remdesivir for Injection Lyophilized Powder for Pediatric Patients Weighing 3.5 kg to Less Than 40 kg

Infusion bag volume	Infusion time	Rate of infusion[a]
100 mL	30 min	3.33 mL/min
	60 min	1.67 mL/min
	120 min	0.83 mL/min
50 mL	30 min	1.67 mL/min
	60 min	0.83 mL/min
	120 min	0.42 mL/min
25 mL	30 min	0.83 mL/min
	60 min	0.42 mL/min
	120 min	0.21 mL/min

a. Note: Rate of infusion may be adjusted based on total volume to be infused.

2.9 Storage of Prepared Dosages

Lyophilized Powder
After reconstitution, vials can be stored up to 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) prior to administration or 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]). Dilute within the same day as administration.

Injection Solution
Prior to dilution, equilibrate remdesivir injection to room temperature (20°C to 25°C [68°F to 77°F]). Sealed vials can be stored up to 12 hours at room temperature prior to dilution.

Diluted Infusion Solution
Store diluted remdesivir solution for infusion up to 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

IMPORTANT:
This product contains no preservative. Any unused portion of a single-dose remdesivir vial should be discarded after a diluted solution is prepared. Maintain adequate records showing receipt, use, and disposition of remdesivir. For unused intact vials, maintain adequate records showing disposition of remdesivir; do not discard unused intact vials.

3. DOSAGE FORMS AND STRENGTHS

- Remdesivir for injection, 100 mg: Each single-dose vial of remdesivir for injection,100 mg, contains a sterile, preservative-free white to off-white to yellow lyophilized powder that is to be reconstituted with 19 mL of Sterile Water for Injection and further diluted into 0.9% sodium chloride infusion bag prior to administration by intravenous infusion. Following reconstitution, each vial contains 100 mg/20 mL (5 mg/mL) remdesivir reconcentrated solution.

- Remdesivir injection, 100 mg/20 mL (5 mg/mL): Each single-dose vial of remdesivir injection contains 100 mg/20 mL (5 mg/mL) of remdesivir as a clear, colorless to yellow, aqueous-based concentrated solution that is to be diluted into 0.9% sodium chloride infusion bag prior to administration by intravenous infusion.

4. CONTRAINDICATIONS
Remdesivir is contraindicated in patients with known hypersensitivity to any ingredient of remdesivir *[see Product Description (13)].*

5. WARNINGS AND PRECAUTIONS
There are limited clinical data available for remdesivir. Serious and unexpected adverse events may occur that have not been previously reported with remdesivir use.

5.1 Hypersensitivity Including Infusion-Related and Anaphylactic Reactions
Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed during and following administration of remdesivir. Signs and symptoms may include hypotension, tachycardia, bradycardia, dyspnea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of remdesivir and initiate appropriate treatment. The use of remdesivir is contraindicated in patients with known hypersensitivity to remdesivir *[see Contraindications (4)]*.

5.2 Increased Risk of Transaminase Elevations

Transaminase elevations have been observed in healthy volunteers who received 200 mg of remdesivir followed by 100 mg doses for 5-10 days. Transaminase elevations have also been reported in patients with COVID-19 who received remdesivir in clinical trials. As transaminase elevations have been reported as a component of COVID-19, including in patients receiving placebo in clinical trials of remdesivir, discerning the contribution of remdesivir to transaminase elevations in this patient population is challenging.

Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir.

- Remdesivir should not be initiated in patients with ALT greater than or equal to 5 times the upper limit of normal at baseline.
- Remdesivir should be discontinued in patients who develop:
    - ALT greater than or equal to 5 times the upper limit of normal during treatment with remdesivir. Remdesivir may be restarted when ALT is less than 5 times the upper limit of normal.
      OR
    - ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.

5.3 Risk of Reduced Antiviral Activity When Coadministered with Chloroquine or Hydroxychloroquine

Coadministration of remdesivir and chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on in vitro data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of remdesivir *[see Drug Interactions (10), Microbiology/Resistance Information (15)].*

6. OVERALL SAFETY SUMMARY

Completion of FDA MedWatch Form to report all medication errors and adverse events occurring during remdesivir treatment is mandatory. Please see the ADVERSE REACTIONS AND MEDICATION ERRORS REPORTING REQUIREMENTS AND INSTRUCTIONS section below for details on FDA MedWatch reporting.

In healthy subjects and hospitalized patients with PCR-confirmed SARS-CoV-2 infection, graded elevations in ALT and AST have been observed with a loading dose of remdesivir 200 mg administered intravenously on Day 1 followed by 100 mg administered intravenously once daily for up to 9 days. The mechanism of these elevations is unknown.

Patients should have appropriate clinical and laboratory monitoring to aid in early detection of any potential adverse events. The decision to continue or

discontinue remdesivir after development of an adverse event should be made based on the clinical risk benefit assessment for the individual.

6.1 Clinical Trials Experience

Clinical Studies in Healthy Adults

Remdesivir was evaluated in four Phase 1 studies in 138 healthy adult volunteers (Studies GS-US-399-1812, GS-US-399-1954, GS-US-399-4231, and GS-US-399-5505). In these studies, transient graded elevations in ALT and AST were observed at repeated once-daily doses of remdesivir.

NIAID ACTT-1 Trial

In a randomized, double-blind, placebo-controlled clinical trial (ACTT-1) of remdesivir in 1,063 hospitalized subjects with COVID-19 treated with remdesivir (n=541) or placebo (n=522) for 10 days, serious adverse events (SAEs) were reported in 21% and 27% of subjects, respectively, and Grade ≥3 non-serious adverse events were reported in 29% and 33% of subjects, respectively. The most common SAE was respiratory failure reported in 5% of subjects treated with remdesivir and 8% of subjects treated with placebo. The most common Grade ≥3 non-serious adverse events in the remdesivir treatment arm are shown in Table 7.

Table 7: Most Common Grade ≥3 Non-Serious Adverse Events in Subjects Receiving Remdesivir—NIAID ACTT-1 Trial

n (%)	**Remdesivir** N=538	**Placebo** N=521
Anemia or decreased hemoglobin	43 (8%)	47 (9%)
Acute kidney injury, decreased eGFR or creatinine renal clearance, or increased blood creatinine	40 (7%)	38 (7%)
Pyrexia	27 (5%)	17 (3%)
Hyperglycemia or increased blood glucose	22 (4%)	17 (3%)
Increased transaminases, including ALT and/or AST	22 (4%)	31 (6%)

Study GS-US-540-5773

In a randomized, open-label clinical trial (Study GS-US-540-5773) of remdesivir in 397 hospitalized subjects with severe COVID-19 treated with remdesivir for 5 (n=200) or 10 days (n=197), adverse events were reported in 70% and 74% of subjects, respectively, SAEs were reported in 21% and 35% of subjects, respectively, and Grade ≥3 adverse events were reported in 30% and 43% of subjects, respectively. The most common adverse events were nausea (10% in the 5-day group vs 9% in the 10-day group), acute respiratory failure (6% vs 11%), ALT increased (6% vs 8%), and constipation (7% in both groups). Nine (4%) subjects in the 5-day group and 20 (10%) subjects in the 10-day group

discontinued treatment due to an adverse event. All-cause mortality at Day 28 was 10% vs 13% in the 5- and 10-day treatment groups, respectively.

6.2 Hepatic Adverse Reactions

Clinical Trials Experience

Experience in Healthy Volunteers

Grade 1 and 2 transaminase elevations were observed in healthy volunteers in Study GS-US-399-5505 (200 mg followed by 100 mg dosing for 5–10 days) and Study GS-US-399-1954 (150 mg daily for 7 or 14 days), which resolved after discontinuation of remdesivir.

Experience in Subjects with COVID-19

NIAID ACTT-1 trial

Grade ≥3 non-serious adverse events of increased aminotransferase levels including ALT, AST, or both were reported in 4% of subjects receiving remdesivir compared with 6% receiving placebo.

Study GS-US-540-5773

Grade ≥3 hepatic laboratory abnormalities reported in subjects treated with remdesivir for 5 (n=200) or 10 days (n=197) are shown in Table 8.

Table 8: Hepatic Laboratory Abnormalities—Study GS-US-540-5773

n/N (%)		**Remdesivir for 5 Days**	**Remdesivir for 10 Days**	**Total**
ALT Increased	Grade 3	8/194 (4%)	11/191 (6%)	19/385 (5%)
	Grade 4	4/194 (2%)	5/191 (3%)	9/385 (2%)
AST Increased	Grade 3	11/194 (6%)	7/190 (4%)	18/384 (5%)
	Grade 4	3/194 (2%)	4/190 (2%)	7/384 (2%)
Total Bilirubin Increased	Grade 3	1/193 (1%)	3/190 (2%)	4/383 (1%)
	Grade 4	0	1/190 (1%)	1/383 (<1%)

Compassionate Use Experience

In the compassionate use program in patients with severe or critical illness with COVID-19, liver function test abnormalities were reported in 12% (19/163) of patients. Time to onset from first dose ranged from 1-16 days. Four of these

patients discontinued remdesivir treatment with elevated transaminases occurring on Day 5 of remdesivir treatment as per protocol.

Seven cases of serious liver-related laboratory abnormality were identified. There was one SAE of blood bilirubin increased in a critically ill patient with septic shock and multiorgan failure. None of the other cases had reported adverse events suggestive of hyperbilirubinemia or symptoms of hepatitis.

7. PATIENT MONITORING RECOMMENDATIONS

Given the limited experience with remdesivir at the recommended dose and duration, patients should have appropriate clinical and laboratory monitoring to aid in early detection of any potential adverse events while receiving remdesivir *[see Dosage and Administration (2.1)]*. **Additionally, completion of FDA MedWatch Form to report all medication errors and serious adverse events is <u>mandatory</u>.**

For mandatory reporting requirements, please see "**MANDATORY REQUIREMENTS FOR REMDESIVIR ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION"** above.

8. ADVERSE REACTIONS AND MEDICATION ERRORS REPORTING REQUIREMENTS AND INSTRUCTIONS

See Overall Safety Summary (Section 6) for additional information.

The prescribing health care provider and/or the provider's designee are/is responsible for the mandatory reporting of all medication errors and the following selected adverse events occurring during remdesivir use and considered to be potentially attributable to remdesivir. These adverse events must be reported within 7 calendar days from the onset of the event:

- Deaths
- Serious Adverse Events

  Serious Adverse Events are defined as:
  - death;
  - a life-threatening adverse event;
  - inpatient hospitalization or prolongation of existing hospitalization;
  - a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
  - a congenital anomaly/birth defect;
  - a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

If a serious and unexpected adverse event occurs and appears to be associated with the use of remdesivir, the prescribing health care provider and/or the

provider's designee should complete and submit a MedWatch form to FDA using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
- Use a postage-paid Form FDA 3500 (available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf) and returning by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787), or by fax (1-800-FDA-0178), or
- Call 1-800-FDA-1088 to request a reporting form

IMPORTANT: When reporting adverse events or medication errors to MedWatch, please complete the entire form with detailed information. It is important that the information reported to FDA be as detailed and complete as possible. Information to include:

- Patient demographics (e.g., patient initials, date of birth)
- Pertinent medical history
- Pertinent details regarding admission and course of illness
- Concomitant medications
- Timing of adverse event(s) in relationship to administration of remdesivir
- Pertinent laboratory and virology information
- Outcome of the event and any additional follow-up information if it is available at the time of the MedWatch report. Subsequent reporting of follow-up information should be completed if additional details become available.

The following steps are highlighted to provide the necessary information for safety tracking:

1. In section A, box 1, provide the patient's initials in the Patient Identifier
2. In section A, box 2, provide the patient's date of birth
3. In section B, box 5, description of the event:
    a. Write "Remdesivir EUA" as the first line
    b. Provide a detailed report of medication error and/or adverse event. It is important to provide detailed information regarding the patient and adverse event/medication error for ongoing safety evaluation of this unapproved drug. Please see information to include listed above.
4. In section G, box 1, name and address:
    a. Provide the name and contact information of the prescribing health care provider or institutional designee who is responsible for the report.
    b. Provide the address of the treating institution (NOT the health care provider's office address).

9. OTHER REPORTING REQUIREMENTS

In addition please provide a copy of all FDA MedWatch forms to:
Gilead Pharmacovigilance and Epidemiology
Fax: 1-650-522-5477
E-mail: Safety_fc@gilead.com

10. DRUG INTERACTIONS

Drug-drug interaction trials of remdesivir and other concomitant medications have not been conducted in humans. Due to antagonism observed in vitro, concomitant use of remdesivir with chloroquine phosphate or hydroxychloroquine sulfate is not recommended *[see Warnings and Precautions (5.3), Microbiology/resistance information (15)]*.

In vitro, remdesivir is a substrate for drug metabolizing enzymes CYP2C8, CYP2D6, and CYP3A4, and is a substrate for Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and P-glycoprotein (P-gp) transporters. In vitro, remdesivir is an inhibitor of CYP3A4, OATP1B1, OATP1B3, BSEP, MRP4, and NTCP. The clinical relevance of these in vitro assessments has not been established.

11. USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

No adequate and well-controlled studies of remdesivir use in pregnant women have been conducted. Remdesivir should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus.

In nonclinical reproductive toxicity studies, remdesivir demonstrated no adverse effect on embryofetal development when administered to pregnant animals at systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) that were 4 times (rats and rabbits) the exposure in humans at the recommended human dose (RHD) (*see Data*).

Animal Data

Remdesivir was administered via intravenous injection to pregnant rats and rabbits (up to 20 mg/kg/day) on Gestation Days 6 through 17, and 7 through 20, respectively, and also to rats from Gestation Day 6 to Lactation/Post-partum Day 20. No adverse effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed in rats and rabbits at nontoxic doses in pregnant animals. During organogenesis, exposures to the predominant circulating metabolite (GS-441524) were 4 (rats and rabbits) times higher than the exposure in humans at the RHD. In a pre/postnatal development study, exposures to the predominant circulating metabolite of remdesivir (GS-441524) were similar to the human exposures at the RHD.

11.2 Nursing Mothers

Risk Summary

There is no information regarding the presence of remdesivir in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies, remdesivir and metabolites have been detected in the nursing pups of mothers given remdesivir, likely due to the presence of remdesivir in milk. Because of the potential for viral transmission to SARS-CoV-2-negative infants and adverse reactions from the drug in breastfeeding infants, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for remdesivir and any potential adverse effects on the breastfed child from remdesivir or from the underlying maternal condition.

Animal Data

Remdesivir and its metabolites were detected in the plasma of nursing rat pups, likely due to the presence of remdesivir and/or its metabolites in milk, following daily intravenous administration of remdesivir to pregnant mothers from Gestation Day 6 to Lactation Day 20. Exposures in nursing pups were approximately 1% that of maternal exposure on lactation day 10.

11.3 Pediatric Use

The safety, effectiveness, or pharmacokinetics of remdesivir for treatment of COVID-19 have not been assessed in pediatric patients. Physiologically-based pharmacokinetics (PBPK) modeling of pharmacokinetic data from healthy adults was used to derive pediatric doses. Pediatric doses are expected to result in comparable steady-state exposures of remdesivir and metabolites as observed in healthy adults following administration of the recommended dosage regimen.

For pediatric patients with weighing 3.5 kg to less than 40 kg, use remdesivir for injection, 100 mg, lyophilized powder only. Remdesivir injection, 100/20 mL (5 mg/mL), should not be used for pediatric patients weighing 3.5 kg to less than 40 kg due to the higher amount of SBECD present and resulting higher tonicity of the solution concentrate compared to the lyophilized formulation *[see Dosage and Administration (2.3 and 2.8)]*.

Pediatric patients (older than 28 days) must have eGFR determined and full-term neonates (at least 7 days to less than or equal to 28 days) must have serum creatinine determined before dosing and daily while receiving remdesivir. Pediatric patients should be monitored for renal function and consideration given for stopping therapy in the setting of substantial decline *[see Dosage and Administration (2.1, 2.5)].*

Because the excipient SBECD is renally cleared and accumulates in patients with decreased renal function, administration of drugs formulated with SBECD (such as remdesivir) is not recommended in adults and pediatric patients (older than 28 days old) with eGFR less than 30 mL/min or in full-term neonates (at

least 7 days and less than or equal to 28 days old) with serum creatinine greater than or equal to 1 mg/dL unless the potential benefit outweighs the potential risk.

11.4 Geriatric Use

The pharmacokinetics of remdesivir have not been evaluated in patients >65 years of age. In general, appropriate caution should be exercised in the administration of remdesivir and monitoring of elderly patients, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

11.5 Renal Impairment

Patients with eGFR greater than or equal to 30 mL/min have received remdesivir for treatment of COVID-19 with no dose adjustment. The safety and efficacy of remdesivir have not been assessed in patients with severe renal impairment or ESRD. The pharmacokinetics of remdesivir have not been evaluated in patients with renal impairment. Remdesivir is not recommended in adults and pediatric patients (at least 28 days old) with eGFR less than 30 mL/min or in full-term neonates (at least 7 days and less than or equal to 28 days old) with serum creatinine greater than or equal to 1 mg/dL unless the potential benefit outweighs the potential risk *[see Dosage and Administration (2.1)].*

Adult and pediatric patients (greater than 28 days old) must have eGFR determined and full-term neonates (at least 7 days to less than or equal to 28 days old) must have serum creatinine determined before dosing and daily while receiving remdesivir.

11.6 Hepatic Impairment

The pharmacokinetics of remdesivir have not been evaluated in patients with hepatic impairment. It is not known if dosage adjustment is needed in patients with hepatic impairment, and remdesivir should only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk *[see Warnings and Precautions (5.2)].*

Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir *[see Dosage and Administration (2.1)]*.

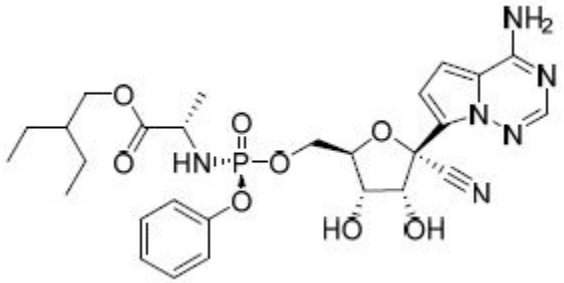
12. OVERDOSAGE

There is no human experience of acute overdosage with remdesivir. Treatment of overdose with remdesivir should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with remdesivir.

13. PRODUCT DESCRIPTION

Remdesivir is a nucleoside ribonucleic acid (RNA) polymerase inhibitor.

The chemical name for remdesivir is 2-ethylbutyl *N*-{(*S*)-[2-*C*-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-2,5-anhydro-d-altrononitril-6-*O*-yl]phenoxyphosphoryl}-L-alaninate. It has a molecular formula of $C_{27}H_{35}N_6O_8P$ and a molecular weight of 602.6 g/mol. Remdesivir has the following structural formula:



13.1 Physical Appearance

Lyophilized Powder

Remdesivir for injection, 100 mg, is a sterile, preservative-free lyophilized powder that is to be reconstituted with 19 mL of Sterile Water for Injection and further diluted into 0.9% sodium chloride infusion bag prior to administration by intravenous infusion. Remdesivir for injection, 100 mg, is supplied in a single-dose clear glass vial.

The appearance of the lyophilized powder is white to off-white to yellow.

Injection Solution

Remdesivir injection, 100 mg/20 mL (5 mg/mL), is a sterile, preservative-free, clear, colorless to yellow, aqueous-based concentrated solution that is to be diluted into 0.9% sodium chloride infusion bag prior to administration by intravenous infusion. Remdesivir injection, 100 mg/20 mL (5 mg/mL), is supplied in a single-dose clear glass vial.

13.2 Inactive Ingredients

The inactive ingredients are sulfobutylether-β-cyclodextrin sodium salt (SBECD), Water for Injection, USP, and may include hydrochloric acid and/or sodium hydroxide for pH adjustment. Remdesivir for injection, 100 mg, contains 3 g SBECD, and remdesivir injection, 100 mg/20 mL (5 mg/mL), contains 6 g SBECD.

14. CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

Remdesivir is an adenosine nucleotide prodrug that distributes into cells where it is metabolized to form the pharmacologically active nucleoside triphosphate metabolite. Metabolism of remdesivir to remdesivir triphosphate has been demonstrated in multiple cell types. Remdesivir triphosphate acts as an analog of adenosine triphosphate (ATP) and competes with the natural ATP substrate for incorporation into nascent RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase, which results in delayed chain termination during replication of the viral RNA. Remdesivir triphosphate is a weak inhibitor of mammalian DNA and RNA polymerases with low potential for mitochondrial toxicity.

14.2 Pharmacokinetics

The pharmacokinetics (PK) of remdesivir have been evaluated in adults in several Phase 1 trials.

- The pharmacokinetics of remdesivir and metabolites have not been in evaluated in patients with COVID-19.
- Following single-dose, 2-hour IV administration of remdesivir solution formulation at doses ranging from 3 to 225 mg, remdesivir exhibited a linear PK profile.
- Following single-dose, 2-hour IV administration of remdesivir at doses of 75 and 150 mg, both the lyophilized and solution formulations provided comparable PK parameters (AUC_{inf}, AUC_{last}, and C_{max}), indicating similar formulation performance.
- Remdesivir 75 mg lyophilized formulation administered IV over 30 minutes provided similar peripheral blood mononuclear cell (PBMC) exposure of the active triphosphate metabolite GS-443902 as remdesivir 150 mg lyophilized formulation administered IV over 2 hours.
- Following a single 150 mg intravenous dose of [^{14}C]-remdesivir, mean total recovery of the dose was >92%, consisting of approximately 74% and 18% recovered in urine and feces, respectively. The majority of remdesivir dose recovered in urine was metabolite GS-441524 (49%), while 10% was recovered as remdesivir.

<u>Specific Populations</u>

Sex, Race and Age

Pharmacokinetic differences based on sex, race, and age have not been evaluated.

Pediatric Patients

The pharmacokinetics of remdesivir in pediatric patients has not been evaluated.

PBPK modeling of pharmacokinetic data from healthy adults was used to derive pediatric doses. PBPK modeling incorporated in vitro data for remdesivir and

other similar compounds along with age-dependent changes in physiology (e.g., organ volume/function, blood flow), metabolism, distribution, and elimination of remdesivir. Pediatric doses are expected to result in comparable steady-state exposures of remdesivir and metabolites as observed in healthy adults following administration of the recommended dosage regimen.

Renal Impairment
Because the excipient SBECD is renally cleared and accumulates in patients with decreased renal function, administration of drugs formulated with SBECD (such as remdesivir) is not recommended in adult and pediatric patients (greater than 28 days old) with eGFR less than 30 mL/min or in full-term neonates (at least 7 days and less than or equal to 28 days old) with serum creatinine greater than or equal to 1 mg/dL unless the potential benefit outweighs the potential risk.

15. MICROBIOLOGY/RESISTANCE INFORMATION

Antiviral Activity

Remdesivir exhibited cell culture antiviral activity against a clinical isolate of SARS-CoV-2 in primary human airway epithelial (HAE) cells with a 50% effective concentration (EC_{50}) of 9.9 nM after 48 hours of treatment. The EC_{50} values of remdesivir against SARS-CoV-2 in Vero cells was 137 nM at 24 hours and 750 nM at 48 hours post-treatment. The antiviral activity of remdesivir was antagonized by chloroquine phosphate in a dose-dependent manner when the two drugs were co-incubated at clinically relevant concentrations in HEp-2 cells infected with respiratory syncytial virus (RSV). Higher remdesivir EC_{50} values were observed with increasing concentrations of chloroquine phosphate. Increasing concentrations of chloroquine phosphate reduced formation of remdesivir triphosphate in normal human bronchial epithelial cells.

Resistance
No clinical data are available on the development of SARS-CoV-2 resistance to remdesivir. The cell culture development of SARS-CoV-2 resistance to remdesivir has not been assessed to date.

Cell culture resistance profiling of remdesivir using the rodent CoV murine hepatitis virus identified 2 substitutions (F476L and V553L) in the viral RNA-dependent RNA polymerase at residues conserved across CoVs that conferred a 5.6-fold reduced susceptibility to remdesivir. The mutant viruses showed reduced viral fitness in cell culture and introduction of the corresponding substitutions (F480L and V557L) into SARS-CoV resulted in 6-fold reduced susceptibility to remdesivir in cell culture and attenuated SARS-CoV pathogenesis in a mouse model.

16. NONCLINICAL TOXICOLOGY

Carcinogenesis
Given the short-term administration of remdesivir for the treatment of COVID-19, long-term animal studies to evaluate the carcinogenic potential of remdesivir are not required.

Mutagenesis
Remdesivir was not genotoxic in a battery of assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes, and in vivo rat micronucleus assays.

Impairment of Fertility
Nonclinical toxicity studies in rats demonstrated no adverse effect on male fertility at exposures of the predominant circulating metabolite (GS-441524) approximately 2 times the exposure in humans at the RHD.

Reproductive toxicity, including decreases in corpora lutea, numbers of implantation sites, and viable embryos, was seen when remdesivir was administered intravenous daily at a systemically toxic dose (10 mg/kg) in female rats 14 days prior to mating and during conception; exposures of the predominant circulating metabolite (GS-441524) were 1.3 times the exposure in humans at the RHD.

Animal Toxicology and/or Pharmacology
Intravenous administration (slow bolus) of remdesivir to male rhesus monkeys at dosage levels of 5, 10, and 20 mg/kg/day for 7 days resulted, at all dose levels, in increased mean urea nitrogen and increased mean creatinine, renal tubular atrophy, and basophilia and casts.

Intravenous administration (slow bolus) of remdesivir to rats at dosage levels of ≥3 mg/kg/day for up to 4 weeks resulted in findings indicative of kidney injury and/or dysfunction.

17. ANIMAL PHARMACOLOGIC AND EFFICACY DATA

It is unknown, at present, how the observed antiviral activity of remdesivir in animal models of SARS-CoV-2 infection will translate into clinical efficacy in patients with symptomatic disease. Key attributes of the remdesivir nonclinical profile supporting its development for the treatment of COVID-19 are provided below:

- Remdesivir showed cell culture antiviral activity against a clinical isolate of SARS-CoV-2 in primary HAE cells (EC_{50} value= 9.9 nM). The EC_{50} values of remdesivir against SARS-CoV-2 in Vero cells has been reported to be 137 nM at 24 hours and 750 nM at 48 hours post-treatment.
- Remdesivir showed antiviral activity in SARS-CoV-2-infected rhesus monkeys. Administration of remdesivir at 10/5 mg/kg (10 mg/kg first dose, followed by 5 mg/kg once daily thereafter) using IV bolus injection initiated 12 hours post-inoculation with SARS-CoV-2 resulted in a reduction in clinical signs of respiratory disease, lung pathology and gross lung lesions, and lung viral RNA levels compared with vehicle-treated animals.

18. CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

Remdesivir is an unapproved antiviral drug with available data from two randomized clinical trials in patients with COVID-19.

Clinical Trials in Subjects with COVID-19

NIAID ACTT-1 Trial in Subjects with Mild/Moderate and Severe COVID-19

A randomized, double-blind, placebo-controlled clinical trial evaluated remdesivir 200 mg once daily for 1 day followed by remdesivir 100 mg once daily for 9 days (for a total of up to 10 days of intravenously administered therapy) in hospitalized adult subjects with COVID-19 with evidence of lower respiratory tract involvement. The trial enrolled 1,063 subjects: 120 [11.3%] subjects with mild/moderate disease and 943 [88.7%] subjects with severe disease. A total of 272 subjects (25.6%) (n=125 received remdesivir) were on mechanical ventilation/ECMO. Subjects were randomized in a 1:1 manner, stratified by disease severity at enrollment, to receive remdesivir (n=541) or placebo (n=522), plus standard of care. The primary clinical endpoint was time to recovery within 28 days after randomization, defined as either discharged from the hospital or hospitalized but not requiring supplemental oxygen and no longer requiring ongoing medical care. In a preliminary analysis of the primary endpoint performed after 607 recoveries were attained (n=1,059; 538 remdesivir, 521 placebo), the median time to recovery was 11 days in the remdesivir group compared to 15 days in the placebo group (recovery rate ratio 1.32; 95% CI 1.12 to 1.55, p<0.001); 14-day mortality was 7.1% for the remdesivir group versus 11.9% for the placebo group (hazard ratio 0.70 [95% CI 0.47, 1.04], p=0.07). Among subjects with mild/moderate disease at enrollment (n=119), the median time to recovery was 5 days in both the remdesivir and placebo groups (recovery rate ratio 1.09; [95% CI 0.73 to 1.62]). Among subjects with severe disease at enrollment (n=940), the median time to recovery was 12 days in the remdesivir group compared to 18 days in the placebo group (recovery rate ratio, 1.37; [95% CI, 1.15 to 1.63]; p<0.001; n=940) and 14-day mortality was 7.7% and 13%, respectively (hazard ratio, 0.71; [95% CI, 0.48 to 1.05]).

Overall, the odds of improvement in the ordinal scale were higher in the remdesivir group at Day 15 when compared to the placebo group (odds ratio, 1.50; [95% CI, 1.18 to 1.91], p=0.001; n=844).

Study GS-US-540-5773 in Subjects with Severe COVID-19
A randomized, open-label multi-center clinical trial (Study GS-US-540-5773) of hospitalized subjects at least 12 years of age with confirmed SARS-CoV-2 infection, oxygen saturation of ≤94% on room air, and radiological evidence of pneumonia compared 197 subjects who received IV remdesivir for 5 days with 200 subjects who received IV remdesivir for 10 days. Patients on mechanical ventilation at screening were excluded. All subjects received 200 mg of remdesivir on Day 1 and 100 mg once daily on subsequent days, plus standard of care. The primary endpoint was clinical status on Day 14 assessed on a 7-point ordinal scale ranging from hospital discharge to increasing levels of oxygen and ventilatory support to death. After adjusting for between-group differences at baseline, patients receiving a 10-day course of remdesivir had similar clinical status at Day 14 as those receiving a 5-day course (odds ratio for improvement: 0.75; [95% CI 0.51 to 1.12]).

Clinical improvement was defined as an improvement of two or more points from baseline on the 7-point ordinal scale. Subjects achieved clinical recovery if they no longer required oxygen support or were discharged from the hospital. At Day 14, observed rates between the 5- and 10-day treatment groups were 65% vs 54% for clinical improvement, 70% vs 59% for clinical recovery, and 8% vs 11% for mortality.

19. HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Lyophilized Powder
Remdesivir for injection, 100 mg, is supplied as a single-dose vial containing a sterile, preservative-free white to off-white to yellow lyophilized powder that is to be reconstituted with 19 mL of Sterile Water for Injection and further diluted into 0.9% sodium chloride infusion bag prior to administration by intravenous infusion. Following reconstitution, each vial contains 100 mg/20 mL (5 mg/mL) remdesivir reconcentrated solution.

Discard unused portion.

The container closure is not made with natural rubber latex.

Injection Solution
Remdesivir injection is supplied as a single dose vial containing 100 mg/20 mL (5 mg/mL) of remdesivir per vial for dilution into 0.9% sodium chloride infusion bag.

Discard unused portion.

The container closure is not made with natural rubber latex.

Storage and Handling

Do not reuse or save unused remdesivir lyophilized powder, injection solution, or diluted solution for infusion for future use. This product contains no preservative.

Lyophilized Powder
Store remdesivir for injection, 100 mg, vials below 30°C (below 86°F) until required for use. Do not use after expiration date.

After reconstitution, vials can be stored up to 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) prior to administration or 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]). Dilute within the same day as administration.

Injection Solution
Store remdesivir injection, 100 mg/20 mL (5 mg/mL), vials at refrigerated temperature (2°C to 8°C [36°F to 46°F]) until required for use. Do not use after expiration date. Dilute within the same day as administration.

Prior to dilution, equilibrate remdesivir injection to room temperature (20°C to 25°C [68°F to 77°F]). Sealed vials can be stored up to 12 hours at room temperature prior to dilution.

Diluted Solution for Infusion
Store diluted remdesivir solution for infusion up to 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

20. PATIENT COUNSELING INFORMATION

SEE *Fact Sheet for Patients and Parents/Caregivers*

21. CONTACT INFORMATION

If you have questions, please contact
www.askgileadmedical.com
1-866-633-4474

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