Remdesivir

Indications/Dosage

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Off-Label

- coronavirus disease 2019 (COVID-19) †
- severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection †

† Off-label indication

This drug may also have activity against the following microorganisms:

severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

NOTE: Some organisms may not have been adequately studied during clinical trials; therefore, exclusion from this list does not necessarily negate the drug's activity against the organism.

INVESTIGATIONAL USE: For the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection†, the virus that causes coronavirus disease 2019 (COVID-19)†

Intravenous dosage

- **Adults requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO)**

  Due to a lack of clinical data, the National Institutes of Health (NIH) COVID-19 treatment guidelines do not give recommendations for or against the use of remdesivir.[65314] 200 mg IV once on day 1 then 100 mg IV once daily for 9 days is suggested by the FDA in the Emergency Use Authorization (EUA) statement.[65364] [65365] This dose is also is being evaluated in multi-center randomized trials.[65128] [65129] [65130] [65131] [65132] [65133] [65245] [65247] [65248]

- **Adults NOT requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO)**

  Due to a lack of clinical data, the National Institutes of Health (NIH) COVID-19 treatment guidelines do not give recommendations for or against the use of remdesivir.[65314] 200 mg IV once on day 1 then 100

mg IV once daily for 4 days in patients with severe disease, defined as a SpO2 of 94% or less on room air or supplemental oxygen, is suggested by the FDA in the Emergency Use Authorization (EUA) statement. May extend treatment for up to 5 additional days if a patient does not demonstrate clinical improvement.[65364] [65365] This dose is also is being evaluated in multi-center randomized trials. [65128] [65129] [65130] [65131] [65132] [65133] [65245] [65247] [65248]

- **Children and Adolescents weighing 40 kg or more requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO)**

  Due to a lack of clinical data, the National Institutes of Health (NIH) COVID-19 treatment guidelines do not give recommendations for or against the use of remdesivir.[65314] 200 mg IV once on day 1 then 100 mg IV once daily for 9 days is suggested by the FDA in the Emergency Use Authorization (EUA) statement.[65364] [65365] Dosing in pediatric patients is based upon physiologically-based (PBPK) modeling and simulation of pharmacokinetic data from healthy adult subjects.[65365]

- **Children and Adolescents weighing 40 kg or more NOT requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO)**

  Due to a lack of clinical data, the National Institutes of Health (NIH) COVID-19 treatment guidelines do not give recommendations for or against the use of remdesivir.[65314] 200 mg IV once on day 1 then 100 mg IV once daily for 4 days in patients with severe disease, defined as a SpO2 of 94% or less on room air or supplemental oxygen, is suggested by the FDA in the Emergency Use Authorization (EUA) statement. May extend treatment for up to 5 additional days if a patient does not demonstrate clinical improvement.[65364] [65365] Dosing in pediatric patients is based upon physiologically-based (PBPK) modeling and simulation of pharmacokinetic data from healthy adult subjects.[65365]

- **Infants, Children, and Adolescents weighing 3.5 to 39 kg requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO)**

  Due to a lack of clinical data, the National Institutes of Health (NIH) COVID-19 treatment guidelines do not give recommendations for or against the use of remdesivir.[65314] 5 mg/kg/dose IV once on day 1 then 2.5 mg/kg/dose IV once daily for 9 days is suggested by the FDA in the Emergency Use Authorization (EUA) statement.[65364] [65365] Dosing in pediatric patients is based upon physiologically-based (PBPK) modeling and simulation of pharmacokinetic data from healthy adult subjects.[65365]

- **Infants, Children, and Adolescents weighing 3.5 to 39 kg NOT requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO)**

  Due to a lack of clinical data, the National Institutes of Health (NIH) COVID-19 treatment guidelines do not give recommendations for or against the use of remdesivir.[65314] 5 mg/kg/dose IV once on day 1 then 2.5 mg/kg/dose IV once daily for 4 days in patients with severe disease, defined as a SpO2 of 94% or less on room air or supplemental oxygen, is suggested by the FDA in the Emergency Use Authorization (EUA) statement. May extend treatment for up to 5 additional days if a patient does not demonstrate clinical improvement.[65364] [65365] Dosing in pediatric patients is based upon physiologically-based (PBPK) modeling and simulation of pharmacokinetic data from healthy adult subjects.[65365]

- **Neonates weighing 3.5 kg or more requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO)**

  Due to a lack of clinical data, the National Institutes of Health (NIH) COVID-19 treatment guidelines do not give recommendations for or against the use of remdesivir.[65314] 5 mg/kg/dose IV once on day 1 then 2.5 mg/kg/dose IV once daily for 9 days is suggested by the FDA in the Emergency Use Authorization (EUA) statement.[65364] [65365] Dosing in pediatric patients is based upon physiologically-based (PBPK) modeling and simulation of pharmacokinetic data from healthy adult subjects.[65365]

- **Neonates weighing 3.5 kg or more NOT requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO)**

  Due to a lack of clinical data, the National Institutes of Health (NIH) COVID-19 treatment guidelines do not give recommendations for or against the use of remdesivir.[65314] 5 mg/kg/dose IV once on day 1 then 2.5 mg/kg/dose IV once daily for 4 days in patients with severe disease, defined as a SpO2 of 94% or less on room air or supplemental oxygen, is suggested by the FDA in the Emergency Use Authorization (EUA) statement. May extend treatment for up to 5 additional days if a patient does not demonstrate clinical improvement.[65364] [65365] Dosing in pediatric patients is based upon physiologically-based (PBPK) modeling and simulation of pharmacokinetic data from healthy adult subjects.[65365]

Maximum Dosage Limits

- Adults

  Safety and efficacy have not been established; however, investigational doses of 200 mg IV on day 1, followed by 100 mg IV once daily have been used.

- Geriatric

  Safety and efficacy have not been established; however, investigational doses of 200 mg IV on day 1, followed by 100 mg IV once daily have been used.

- Adolescents

  Adolescents weighing 40 kg or more: Safety and efficacy have not been established; investigational doses of 200 mg IV on day 1, followed by 100 mg IV once daily have been used.

  Adolescents weighing 39 kg or less: Safety and efficacy have not been established; however, investigational doses of 5 mg/kg/dose IV on day 1, followed by 2.5 mg/kg/dose IV once daily have been used.

- Children

  Children weighing 40 kg or more: Safety and efficacy have not been established; however, investigational doses of 200 mg IV on day 1, followed by 100 mg IV once daily have been used.

  Children weighing 39 kg or less: Safety and efficacy have not been established; however, investigational doses of 5 mg/kg/dose IV on day 1, followed by 2.5 mg/kg/dose IV once daily have been used.

- Infants

  Safety and efficacy have not been established; however, investigational doses of 5 mg/kg/dose IV on day 1, followed by 2.5 mg/kg/dose IV once daily have been used.

- Neonates

  Neonates weighing 3.5 kg or more: Safety and efficacy have not been established; however, investigational doses of 5 mg/kg/dose IV on day 1, followed by 2.5 mg/kg/dose IV once daily have been used.

Neonates weighing less than 3.5 kg: Safety and efficacy have not been established.

Patients with Hepatic Impairment Dosing

It is unknown if dosage adjustments are needed in patients with hepatic disease; therefore, remdesivir should only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk. Avoid treatment in patients with a baseline ALT greater than or equal to 5-times the upper limit of normal (ULN). Discontinue treatment if ALT increases to 5-times ULN or more or if the increase in ALT is accompanied by signs or symptoms of hepatic inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR. [65365]

Patients with Renal Impairment Dosing

Adult and Pediatric patients

eGFR 30 mL/minute or more: No dosage adjustment needed.

eGFR less than 30 mL/minute: Treatment is not recommended unless the potential benefit outweighs the potential risk.[65365]

Term neonates 7 days and older

Serum creatinine less than 1 mg/dL: No dosage adjustment needed.

Serum creatinine 1 mg/dL or more: Treatment is not recommended unless the potential benefit outweighs the potential risk.[65365]

Term neonates younger than 7 days

Recommendations are not available.[65365]

† Off-label indication

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References

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65365 – Food and Drug Administration (FDA). Fact sheet for health care providers: emergency use authorization (EUA) of remdesivir (GS-5734). Retrieved May 1, 2020. Available on the World Wide Web at https://www.fda.gov/media/137566/download.

How Supplied

Remdesivir Powder for solution for injection
Remdesivir 100mg Powder for Injection (61958-0000) (Gilead Sciences Inc)

Remdesivir Solution for injection
Remdesivir 5mg/mL Solution for Injection (Gilead Sciences Inc)

Description/Classification

Description

Remdesivir is an investigational antiviral medication with a broad spectrum of in vitro activity against RNA viruses belonging to *Filoviridae*, *Paramyxoviridae*, *Pneumoviridae*, and *Orthocoronavirinae* families. Due to a lack of clinical data, the National Institutes of Health (NIH) coronavirus disease 2019 (COVID-19) treatment guidelines do not give recommendations for or against the use of remdesivir.[65314] Although not FDA-approved, the FDA has issued an Emergency Use Authorization (EUA) for the use of intravenous remdesivir to treat hospitalized COVID-19 patients with severe disease, defined as a SpO2 of 94% or less on room air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[65364] [65365] It is also available through the Expanded Access or Compassionate Use programs for the treatment of severe COVID-19.[65134] [65156] [65161] Preliminary data from open-label compassionate use in patients with severe disease showed clinical improvement in 36 of 53 patients (68%) with an improvement in oxygen support. By 28 days of follow-up, the cumulative incidence of clinical improvement, as defined by either a decrease of 2 points or more on the 6 point ordinal scale or live discharge was 84%. Clinical improvement was less frequent in those receiving invasive ventilation and in patients 70 years or older.[65245]

Classifications

- General Anti-infectives Systemic
  - Antivirals For Systemic Use
    - Other Systemic Antivirals

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References

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65364 – Food and Drug Administration (FDA). Emergency use of remdesivir for the treatment of hospitalized 2019 coronavirus disease (COVID-19) patients: emergency use authorization letter. Retrieved May 1, 2020. Available on the World Wide Web at https://www.fda.gov/media/137564/download.

65365 – Food and Drug Administration (FDA). Fact sheet for health care providers: emergency use authorization (EUA) of remdesivir (GS-5734). Retrieved May 1, 2020. Available on the World Wide Web at https://www.fda.gov/media/137566/download.

Administration Information

General Administration Information

For storage information, see the specific product information within the study protocols.

NOTE: Prior to administering remdesivir under the Emergency Use Authorization (EUA), the health care provider must communicate to the patient or parent/caregiver information consistent with the "Fact Sheet for Patients and Parents/Caregivers", including:

- Remdesivir has been authorized for emergency use by the FDA. It 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 treatment 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.[65365]

Route-Specific Administration

Injectable Administration

- Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit.

Intravenous Administration

If the patient is enrolled in a clinical trial, follow the specific instructions provided by the study protocol.

Preparation Instructions per Emergency Use Authorization (EUA) [65365]

**Remdesivir products are preservative-free; discard any unused portion of single-dose vials. Prepare solution for infusion on the same day as administration. Maintain records showing receipt, use, and disposition of remdesivir.

Lyophilized Powder Reconstitution:

**For pediatric patients weighing less than 40 kg, use only the lyophilized powder formulation to prepare doses.

- For each 100 mg vial, reconstitute with 19 mL of Sterile Water for Injection to give a concentration of 5 mg/mL.
- Discard the vial if vacuum does not pull the Sterile Water for Injection into the vial.
- Immediately shake 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 for another 30 seconds and then allow to settle for 2 to 3 minutes.
- Repeat this process as needed until the contents are fully dissolved, resulting in a clear solution.
- Further dilution is required prior to administration.
- *Storage:* Store remdesivir lyophilized powder vials below 30 degrees C (below 86 degrees F) until required for use.
    - Total storage time from reconstitution to administration should not exceed 4 hours at room temperature (20 to 25 degrees C; 68 to 77 degrees F) or 24 hours under refrigeration (2 to 8 degrees C; 36 to 46 degrees F).

Injection Solution:

**Do not use to prepare doses for pediatric patients weighing less than 40 kg.

- Remove remdesivir injection solution from refrigerator and allow to come to room temperature (20 to 25 degrees C; 68 to 77 degrees F) before diluting.
- Inspect vial to ensure container closure is free from defects, and the solution is free of particulate matter before use.
- *Storage:* Store remdesivir injection solution under refrigeration (2 to 8 degrees C; 36 to 46 degrees F) until required for use. Sealed vials can be stored up to 12 hours at room temperature before dilution.

Dilution:

Dilution for 200 mg Loading Dose:

- From a 250 mL infusion bag of 0.9% NaCl Injection, withdraw and discard 40 mL.
- Transfer 40 mL remdesivir 5 mg/mL solution from vials to the 0.9% NaCl Injection infusion bag.
    - If using remdesivir injection solution (not reconstituted powder), inject approximately 10 mL of air into the remdesivir vial above the solution level before withdrawing dose to facilitate withdrawal.
- Gently invert bag 20 times to mix solution. Do not shake.
- *Storage:* The prepared solution is stable for 4 hours at room temperature (20 to 25 degrees C; 68 to 77 degrees F) or 24 hours under refrigeration (2 to 8 degrees C; 36 to 46 degrees F).
    - If prepared using reconstituted lyophilized powder, total storage time from reconstitution to administration should not exceed 4 hours at room temperature or 24 hours under refrigeration.

Dilution for 100 mg Maintenance Doses:

- From a 250 mL infusion bag of 0.9% NaCl Injection, withdraw and discard 20 mL.
- Transfer 20 mL reconstituted remdesivir 5 mg/mL solution from vial to the 0.9% NaCl Injection infusion bag.
- Gently invert bag 20 times to mix solution. Do not shake.
- *Storage:* The prepared solution is stable for 4 hours at room temperature (20 to 25 degrees C; 68 to 77 degrees F) or 24 hours under refrigeration (2 to 8 degrees C; 36 to 46 degrees F).

- If prepared using reconstituted lyophilized powder, total storage time from reconstitution to administration should not exceed 4 hours at room temperature or 24 hours under refrigeration.

Dilution for Pediatric Loading Dose (patients weighing less than 40 kg):

- Use only the reconstituted lyophilized powder formulation.
- Final concentrations for all possible doses are not included in the EUA Fact Sheet. For the doses provided, concentrations range from 0.4 to 1.5 mg/mL.
- Suggested sizes of 0.9% NaCl Injection infusion bag to be used:
  - 25 mL 0.9% NaCl Injection for remdesivir doses of 17.5 mg, 20 mg, and 25 mg
  - 50 mL 0.9% NaCl Injection for remdesivir doses of 37.5 mg and 50 mg
  - 100 mL 0.9% NaCl Injection for remdesivir doses 75 mg, 100 mg, 125 mg, and 150 mg
  - 250 mL 0.9% NaCl Injection for doses of 150 mg and 175 mg

- Calculate the volume of remdesivir 5 mg/mL solution necessary to make the patient's dose.
- From the chosen 0.9% NaCl Injection infusion bag, withdraw and discard the volume of 0.9% NaCl Injection equal to that of the calculated remdesivir solution.
- Transfer the remdesivir 5 mg/mL solution from vial(s) to the 0.9% NaCl Injection infusion bag.
- Gently invert bag 20 times to mix solution. Do not shake.
- *Storage:* The prepared solution is stable for 4 hours at room temperature (20 to 25 degrees C; 68 to 77 degrees F) or 24 hours under refrigeration (2 to 8 degrees C; 36 to 46 degrees F).
  - For solutions prepared using the reconstituted lyophilized powder, total storage time from reconstitution to administration should not exceed 4 hours at room temperature or 24 hours under refrigeration.

Dilution for Pediatric Maintenance Doses (patients weighing less than 40 kg):

- Use only the reconstituted lyophilized powder formulation.
- Final concentrations for all possible doses are not included in the EUA Fact Sheet. For the doses provided, concentrations range from 0.352 to 1 mg/mL.
- Suggested sizes of 0.9% NaCl Injection infusion bag to be used:
  - 25 mL 0.9% NaCl Injection for remdesivir doses of 17.5 mg, 20 mg, and 25 mg
  - 50 mL 0.9% NaCl Injection for remdesivir doses of 37.5 mg and 50 mg
  - 100 mL 0.9% NaCl Injection for remdesivir doses 75 mg, 100 mg, 125 mg, and 150 mg
  - 250 mL 0.9% NaCl Injection for doses of 150 mg and 175 mg

- Calculate the volume of remdesivir 5 mg/mL solution necessary to make the patient's dose.
- From the chosen 0.9% NaCl Injection infusion bag size, withdraw and discard the volume of 0.9% NaCl Injection equal to that of the calculated remdesivir solution.
- Transfer the remdesivir 5 mg/mL solution from vial(s) to the 0.9% NaCl Injection infusion bag.
- Gently invert bag 20 times to mix solution. Do not shake.
- *Storage:* The prepared solution is stable for 4 hours at room temperature (20 to 25 degrees C; 68 to 77 degrees F) or 24 hours under refrigeration (2 to 8 degrees C; 36 to 46 degrees F).
  - For solutions prepared using the reconstituted lyophilized powder, total storage time from reconstitution to administration should not exceed 4 hours at room temperature or 24 hours under refrigeration.

Intermittent IV Infusion:

- Infuse over 30 to 120 minutes.

- After the infusion is complete, flush with at least 30 mL 0.9% NaCl Injection.
- Do not mix with or administer simultaneously with other IV medications.

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References

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Adverse Reactions

- atrial fibrillation
- constipation
- delirium
- diaphoresis
- diarrhea
- ecchymosis
- elevated hepatic enzymes
- headache
- hematuria
- hypernatremia
- hypotension
- infusion-related reactions
- nausea
- phlebitis
- rash
- shivering
- vomiting

Safety data from controlled trials are not available. The safety profile of remdesivir is incompletely characterized; serious and unexpected adverse events may occur that have not yet been reported. Health care providers administering remdesivir under the Emergency Use Authorization must report all medication errors and serious adverse events to the FDA within 7 calendar days of occurrence.[65365]

Infusion-related reactions have occurred during remdesivir infusion; monitor patients during administration. If a clinically significant reaction occurs, immediately discontinue the infusion and initiate appropriate treatment. Reactions may include low blood pressure, nauseous feeling, vomiting, diaphoresis, and shivering.[65365]

In an open-label compassionate-use study of remdesivir used in patients with severe COVID-19 (n = 53), hypotension was reported in 8% of patients.[65245] In a study of patients treated for Ebola virus disease, one patient had a hypotensive episode during the administration of the loading dose of remdesivir, which lead to a fatal cardiac arrest; however, the independent pharmacovigilance committee noted that the death could not be readily distinguished from underlying fulminant Ebola virus disease.[65247]

In an open-label compassionate-use study of remdesivir used in patients with severe COVID-19 (n = 53), atrial fibrillation was reported in 6% of patients.[65245]

In pooled data from Gilead-sponsored studies (n = 138), constipation was reported in 7 patients and nausea was reported in 5 patients.[65247] In an open-label compassionate-use study of remdesivir used in patients with severe COVID-19 (n = 53), diarrhea was reported in 9% of patients.[65245]

In the compassionate-use program of patients with severe COVID-19, elevated hepatic enzymes were reported in 11.7% (n = 19/163) of remdesivir recipients. The time to onset from the first dose ranged from 1 to 16 days. Treatment was discontinued in 4 patients as per protocol. Serious hepatic-related laboratory abnormalities were

identified in 7 patients, and 1 serious adverse event (SAE) of increased blood bilirubin was reported 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. In patients with severe COVID-19, it may be difficult to attribute hepatotoxicity to remdesivir rather than the underlying disease; however, mild to moderate (Grade 1 and 2) elevated hepatic enzymes have also been associated with the use of remdesivir in healthy volunteers and in patients infected with the Ebola virus.[65245] [65365] Transient treatment-emergent elevations in AST and ALT were observed during studies in healthy volunteers. None of these elevations were graded in single-ascending dose studies and all were Grade 1 or 2 in multiple-dose studies. Some ALT and AST elevations were associated with graded prothrombin time (PT) elevations; however, there were no graded changes in INR.[65247] Hepatotoxicity is an identified risk.[65248]

In an open-label compassionate-use study of remdesivir used in patients with severe COVID-19 (n = 53), 6% of patients had hypernatremia.[65245]

Nonclinical toxicology studies have shown renal abnormalities with remdesivir; however, clear evidence of nephrotoxicity has not been reported. In an open-label compassionate-use study of remdesivir used in patients with severe COVID-19 (n = 53), renal adverse events reported included acute renal injury (6%), renal impairment (8%), and hematuria (4%).[65245]

In pooled data from Gilead-sponsored studies (n = 138), phlebitis was reported in 8 patients.[65247]

In pooled data from Gilead-sponsored studies (n = 138), ecchymosis was reported in 5 patients.[65247]

In an open-label compassionate-use study of remdesivir used in patients with severe COVID-19 (n = 53), rash was reported in 8% of patients.[65245]

In pooled data from Gilead-sponsored studies (n = 138), headache was reported in 6 patients and extremity pain was reported in 5 patients.[65247]

In an open-label compassionate-use study of remdesivir used in patients with severe COVID-19 (n = 53), 4% of patients had delirium.[65245]

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References

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Contraindications/Precautions

Absolute contraindications are italicized.

- *dialysis*
- *renal failure*
- breast-feeding
- hepatic disease
- infusion-related reactions
- pregnancy
- renal impairment

There are limited clinical data available for remdesivir; serious and unexpected adverse events may occur that have not yet been reported. Health care providers administering remdesivir under the Emergency Use Authorization must report all medication errors and serious adverse events to the FDA within 7 calendar days of occurrence.[65365]

Remdesivir is contraindicated in patients with *hypersensitivity to remdesivir*.[65247][65248][65365]

Study protocols for remdesivir exclude patients with evidence of multiorgan failure and the use of more than 1 pressor for septic shock. This contraindication is based on a lack of safety data for patients with end-organ failure. However, once a patient initiates treatment with remdesivir, subsequent use of pressors is not a reason for discontinuation. The use of 1 pressor at low/medium doses for inotropic support due to the use of sedation and paralytics while on the ventilator is allowed.[65247][65248]

Infusion-related reactions have occurred during remdesivir infusion; monitor patients during administration. If a clinically significant reaction occurs, immediately discontinue the infusion and initiate appropriate treatment. Reactions may include hypotension, nausea, vomiting, diaphoresis, and shivering.[65365]

All potential recipients of remdesivir must have an estimated glomerular filtration rate (eGFR) determined prior to drug administration. Treatment with remdesivir is not recommended in adult and pediatric patients with an eGFR less than 30 mL/minute or in term neonates 7 days and older with serum creatinine greater than or equal to 1 mg/dL unless the potential benefit outweighs the potential risk. Recommendations are not available for term neonates younger than 7 days.[65365] Study protocols contraindicate the use of remdesivir in patients with *severe renal impairment* (eGFR less than 30 mL/minute), *renal failure*, and in *patients receiving dialysis or continuous renal replacement therapy*. Both IV formulations of remdesivir contain sulfobutyl ether beta-cyclodextrin sodium (SBECD) as a solubility enhancer. SBECD is renally cleared and accumulates in patients with decreased renal function.[65247] [65248]

It is unknown if dosage adjustments are needed in patients with hepatic disease; therefore, remdesivir should only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk. Conduct liver function testing (LFT) in all patients before starting remdesivir and daily while receiving remdesivir. Avoid starting treatment in patients with a baseline ALT greater than or equal to 5-times the upper limit of normal (ULN). For elevated hepatic enzymes developing during therapy, discontinue treatment if the increase in ALT is accompanied by signs or symptoms of hepatic inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR or the ALT increases to 5-times ULN or more. Remdesivir may be restarted when ALT drops below 5-times ULN.[65365]

There are no data regarding the use of remdesivir during pregnancy to determine the drug-associated risk for major birth defects, miscarriages, or adverse maternal or fetal outcomes. Study protocols state the use of

remdesivir in pregnant women is not recommended based on lack of safety data; however, remdesivir has been used from the treatment of Ebola in a few pregnant women.[65247] [65248] In animal studies involving rats and rabbits, no adverse effects on embryofetal development were observed following exposure to the predominant circulating metabolite (GS-441524) that were 4-times the exposure at the recommended human dose. Administer during pregnancy only if the potential benefit to the mother justifies the potential risks to the fetus.[65365]

There are no data regarding the presence of remdesivir in human milk, the effects on the breast-fed infant, or the effects on milk production. Consider the benefits of breast-feeding, the risk of potential infant drug exposure, the potential for viral transmission to SARS-CoV-2-negative infants, and the risk of an untreated or inadequately treated condition. If a breast-feeding infant experiences an adverse effect related to a maternally administered drug, health care providers are encouraged to report the adverse effect to the FDA.[65248] [65365]

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Mechanism of Action

Remdesivir is a monophosphoramidate prodrug of remdesivir-triphosphate (RDV-TP), an adenosine analog that acts as an inhibitor of RNA-dependent RNA polymerases (RdRps). Remdesivir-TP competes with adenosine-triphosphate for incorporation into nascent viral RNA chains. Once incorporated into the viral RNA at position i, RDV-TP terminates RNA synthesis at position i+3. Because RDV-TP does not cause immediate chain termination (i.e., 3 additional nucleotides are incorporated after RDV-TP), the drug appears to evade proofreading by viral exoribonuclease (an enzyme thought to excise nucleotide analog inhibitors). Remdesivir causes delayed RNA chain termination during the process of viral replication.

Remdesivir has a broad spectrum of in vitro antiviral activity against RNA viruses, including viruses belonging to *Filoviridae*, *Paramyxoviridae*, *Pneumoviridae*, and *Orthocoronavirinae* families. The 50% effective concentration (EC_{50}) against a clinical isolate of SARS-CoV-2 in primary human airway epithelial (HAE) cells is 9.9 nM after 48 hours of treatment. The EC_{50} against SARS-CoV-2 in Vero cells at 24 hours and 48 hours post-treatment are 137 nM and 750 nM, respectively. No clinical data are available regarding the development of SARS-CoV-2 resistance to remdesivir.[65120] [65133] [65134] [65135] [65136] [65137] [65156] [65161] [65247] [65248] [65365]

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Pharmacokinetics

Remdesivir is administered intravenously. Remdesivir is a single diastereomer monophosphoramidate prodrug of a monophosphate nucleoside analog (GS-441524). Remdesivir has moderate protein binding, with a free fraction in humans of 12.1%.[65247]

Preliminary data show that remdesivir is extensively metabolized. The rapid decline in remdesivir plasma concentrations is accompanied by the sequential appearance of the intermediate metabolite GS-702477 and the nucleoside metabolite GS-44152. Within cells, the GS-44152 monophosphate undergoes rapid conversion to the pharmacologically active analog of adenosine triphosphate, GS-443902. Although remdesivir is a substrate of CYP2C8, CYP2D6, and CYP3A4, metabolism is likely to be predominantly mediated by hydrolase activity. Metabolism of the metabolites has not been reported. In radiolabeled studies, the total combined mean recovery of [14C]-radioactivity in feces and urine was approximately 92%, with most of the radioactive dose recovered from the urine (approximately 74%). Unchanged remdesivir is not present in the urine to any substantial extent, but its main metabolite, GS-441524, is found in urine. GS-44152 was predominately recovered in the urine (49%), with remdesivir (10%) and other metabolites (6%) accounting for less of the total radioactive dose.[65365] In single-dose studies in healthy adults, the half-life ranged from 0.66 to 1.05 hours. After multiple doses, the half-life was consistent at approximately 1 hour. The half-life of the metabolite GS-44152 was approximately 24.5 hours. Based on peripheral blood mononuclear cell pharmacokinetic parameters, the half-life for metabolite GS-443902 ranged from 35.95 to 48.79 hours. Based on peripheral blood mononuclear cell pharmacokinetic parameters, the half-life for metabolite GS-4431524 ranged from 32.23 to 48.38 hours.[65247]

Affected cytochrome P450 isoenzymes and drug transporters: CYP2C8, CYP2D6, CYP3A4, OATP1B1, OATP1B3, BSEP, MRP4, NTCP, P-gp

In vitro, remdesivir is a substrate for CYP2C8, CYP2D6, CYP3A4, and the transporters organic anion transporting polypeptide 1B1 (OATP1B1) and p-glycoprotein (P-gp). The impact of the transporters on remdesivir disposition is likely minimized by the parenteral route of administration. Remdesivir is an in vitro inhibitor of CYP3A4 and the transporters OATP1B1, OATP1B3, bile salt export pump (BSEP), multidrug resistance protein 4 (MRP4), and sodium taurocholate cotransporting polypeptide (NTCP); however, its potential to be the perpetrator of clinically significant interactions is limited by its rapid clearance. Hepatocyte donor-dependent induction of mRNA levels of CYP1A2 and CYP2B6 was observed.[65247]

Some in vitro interaction results may indicate a potential for drug interactions, but in vivo relevance is likely low given the transient exposure to remdesivir after IV infusion. The interaction potential of metabolites is largely unknown.[65247]

Route-Specific Pharmacokinetics

- **Oral Route**

  Remdesivir is not suitable for oral delivery due to significant first-pass clearance.[65247]

- **Intravenous Route**

  Remdesivir and its major metabolite, GS-441524, exhibit a linear pharmacokinetic profile. Both the lyophilized formulation and the IV solution formulation provided comparable remdesivir pharmacokinetic parameters.[65365] After a single dose in healthy adults, the AUC_{0-24} values were 4.8 microM x hour for remdesivir and 7.7 microM x hour for GS-441524. The Tmax for remdesivir after a single dose was approximately 2 hours. Pharmacokinetic parameters after multiple doses were consistent with those observed with single-dose administration.[65247]

Special Populations

- **Hepatic Impairment**

  There are no data available on the pharmacokinetics of remdesivir in patients with hepatic impairment.[65247] [65365]

- **Renal Impairment**

  There are no data available on the pharmacokinetics of remdesivir in patients with renal impairment. [65365] Both IV formulations of remdesivir contain sulfobutyl ether beta-cyclodextrin sodium (SBEDC) as a solubility enhancer. SBEDC is renally cleared and accumulates in patients with decreased renal function. The main metabolite for remdesivir, GS-441524, may theoretically increase in patients with impaired renal function.[65247]

- **Pediatrics**

  For pediatric patients weighing 40 kg or more, administration of the recommended adult dosing regimen is expected to produce exposures of both remdesivir and the major metabolite, GS-441524, that are within the expected adult steady-state exposure range. In pediatric patients weighing 3.5 to 39 kg, the recommended weight-based dosing regimen is expected to produce remdesivir exposures that are comparable to those observed in adults while limiting the exposure of GS-441524 in very young children.[65365]

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Pregnancy/Breast-feeding

Pregnancy

There are no data regarding the use of remdesivir during pregnancy to determine the drug-associated risk for major birth defects, miscarriages, or adverse maternal or fetal outcomes. Study protocols state the use of remdesivir in pregnant women is not recommended based on lack of safety data; however, remdesivir has been used from the treatment of Ebola in a few pregnant women.[65247] [65248] In animal studies involving rats and rabbits, no adverse effects on embryofetal development were observed following exposure to the predominant circulating metabolite (GS-441524) that were 4-times the exposure at the recommended human dose. Administer during pregnancy only if the potential benefit to the mother justifies the potential risks to the fetus.[65365]

Breast-Feeding

There are no data regarding the presence of remdesivir in human milk, the effects on the breast-fed infant, or the effects on milk production. Consider the benefits of breast-feeding, the risk of potential infant drug exposure, the potential for viral transmission to SARS-CoV-2-negative infants, and the risk of an untreated or inadequately treated condition. If a breast-feeding infant experiences an adverse effect related to a maternally administered drug, health care providers are encouraged to report the adverse effect to the FDA.[65248] [65365]

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Interactions

No information is available regarding drug interactions associated with Remdesivir - refer to Remdesivir prescribing information.

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Monitoring Parameters

- CBC with differential
- LFTs
- serum creatinine/BUN
- serum electrolytes

US Drug Names

Global Drug names