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| Remdesivir (Veklury®) – Provider Education |
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[Additional resources](#_Additional_Resources:)   **Mechanism of action**   * Direct acting nucleotide inhibitor of the SARS-CoV-2 RNA dependent RNA polymerase that causes premature termination of viral RNA transcription.   **Indication**   * Indicated for the *treatment of COVID-19* in adult and pediatric patients (> 28 days old and weighing > 3kg) with a positive SARS-CoV-2 viral test or with clinically suspected COVID-19 (based on symptoms and potential exposures) when a test is not available, that are:   + Hospitalized OR   + Non-hospitalized, presenting with mild-to-moderate COVID-19 and high risk for progression (based on [CDC criteria](https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html)) to severe COVID-19, hospitalization, or death  Guideline Recommended Use  *(current as of 8/2023; refer to individual guidelines for up to date information)*  |  |  | | --- | --- | | [NIH](https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/remdesivir/) | Adults   * Non-hospitalized adults with mild-to-moderate COVID-19 at [high risk for clinical progression](https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html) (3-day course), as an alternative to nirmatrelvir/ritonavir (Paxlovid™) * Hospitalized patients not requiring oxygen supplementation who are [high risk for clinical progression](https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html) (5-day course) * Hospitalized patients requiring conventional oxygen supplementation, combined with dexamethasone if more than minimal oxygen supplementation (5-day course) * Hospitalized patients who require HFNC or non-invasive ventilation receiving immunomodulatory therapy, for certain patients (immunocompromised, evidence of ongoing replication, patients who are within 10 days of symptom onset).   Pediatrics   * Non-hospitalized children (aged > 12 years) with mild-to-moderate COVID-19 at [high risk for clinical progression](https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html) (3-day course), as an alternative to nirmatrelvir/ritonavir * Hospitalized children (> 12 years) not requiring oxygen supplementation who are at [high risk for clinical progression](https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html) (5-day course) * Hospitalized children (> 28 days weighing > 3kg) requiring oxygen supplementation, combined with dexamethasone if increasing oxygen needs or if requiring oxygen through high-flow device or non-invasive ventilation | | [IDSA](https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#Recommendations15-17:Remdesivir) | Adults/Pediatrics   * Among patients (ambulatory or hospitalized) with mild-to-moderate COVID-19 at [high risk for clinical progression](https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html), remdesivir should be initiated within 7 days of symptom onset (3-day regimen) * In patients on supplemental oxygen but **not** on mechanical ventilation or ECMO, treatment with 5-days of remdesivir is recommended * In hospitalized patients with severe COVID-19 (SpO2 < 94% on RA), remdesivir is recommended over no antiviral treatment * In hospitalized patients on invasive ventilation (including mechanical ventilation) and/or ECMO, recommend against the routine use of remdesivir | | [WHO](https://www.who.int/teams/health-care-readiness/covid-19) | Adults/Pediatrics   * Non-severe COVID-19 at highest risk for hospitalization (e.g. lack of vaccination, older people, immunodeficiency, chronic diseases) (3-day regimen) * Severe COVID-19 (5-day regimen), not recommended for critical illness\* |   \*[WHO](https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2023.1) definition for severe disease (SpO2 <90% on RA, signs of pneumonia, signs of severe respiratory distress) and critical disease (requires life-sustaining treatment, acute respiratory distress syndrome, sepsis, septic shock)  **Dosing, Duration, Monitoring**  Dosing & Duration Recommendations   |  | | --- | | **Adult and Pediatric patients > 12 years and weighing at least 40kg\*** | | * + **Severe COVID-19**, requiring hospitalization (*5-day regimen*)     - 200mg IV x1 dose on day 1, followed by 100mg IV once daily on days 2 through 5ꝉ,§   + **Mild-to-moderate COVID-19**, not requiring hospitalization (*3-day regimen*)     - 200mg IV x1 dose on day 1, followed by 100mg IV once daily on days 2 and 3 | | **Pediatric patients > 28 days to 11 years weighing 3kg to <40kg\*** | | * + **Severe COVID-19**, requiring hospitalization (*5-day regimen*)     - 5 mg/kg IV on day 1, followed by 2.5mg/kg IV once daily on days 2 through 5ꝉ,§   + **Mild-to-moderate COVID-19** not requiring hospitalization (*3-day regimen*)     - 5mg/kg IV on day 1, followed by 2.5mg/kg once daily on days 2 and 3 |   \**There are no dosage adjustments recommended/required for renal or hepatic dysfunction, however per manufacturer guidance use is not recommended if ALT >10x ULN or if ALT elevation accompanied by signs/symptoms liver inflammation*  ꝉ *Or until discharge, whichever comes first*  § *Manufacturer prescribing information recommends 10 days duration for those requiring mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) (NIH guidelines do not recommend use in this setting), and consideration of extending 5-day courses an additional 5 days if poor clinical response for those not requiring mechanical ventilation or ECMO. For patients requiring HFNC or non-invasive ventilation also receiving immunomodulator therapy given remdesivir, NIH guidance recommends the consideration to extend the course beyond 5 days based on clinical response.*  Monitoring Requirements/Recommendations   * SARS-CoV-2 Viral test (positive Antigen or positive PCR) prior initiation of therapy   + While a positive test is not required prior to starting therapy, it is recommended if available, to confirm the diagnosis of COVID-19 with viral testing prior to initiating therapy * Liver function tests (baseline and while on therapy as clinically appropriate) * Prothrombin time (PTT, baseline and while on therapy as clinically appropriate)   **Safety**   * Adverse reactions   + Most common adverse reactions (>5%): nausea, ALT increase, AST increase, PTT increase     - Therapy should be discontinued if ALT is >10x ULN or if ALT elevation is accompanied by signs/symptoms of liver inflammation   + Less common adverse reactions (<5%): bradycardia, hypersensitivity reactions, rash, generalized seizure * Drug-drug interactions   + Avoid concomitant administration with hydroxychloroquine and chloroquine (potential antagonism)   + While remdesivir and its metabolites have been identified *in vitro* as substrates of CYP3A4, OATP1B1, and P-glycoprotein transporters, and can inhibit CYP3A4 and OATP1B1; the clinical significance is unknown. Per manufacturer [prescribing information](https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf), there are no clinically significant drug interactions with inducers of CYP3A4 or inhibitors of OATP1B1 and P-glycoprotein * Severe Renal Impairment (eGFR <30 ml/min)   + The FDA in July 2023 approved the use of remdesivir in the setting of severe renal impairment, including those on dialysis. With this approval, there is no longer the requirement to determine eGFR prior to initiation of therapy. * Pregnancy   + Available data have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes following exposure in the second or third trimester. There are insufficient data to evaluate the risk during the first trimester. See [manufacturer prescribing information](https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf) for additional information.   + A non-randomized, open-label clinical study (IMPAACT 2032) found no clinically relevant differences in the PK of remdesivir or its metabolites in pregnant (median gestational age 28 weeks) vs. non-pregnant patients, no differences are expected between the first and second/third trimesters.   + A [compassionate use study](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7797739/) found that remdesivir was well tolerated with a low incidence of serious adverse events. A [recent review](https://academic.oup.com/jac/article/77/1/24/6356837) also summarizes relevant information pertaining to use in the setting of pregnancy.   + Non-clinical reproductive studies in animals found no adverse effect on embryo-fetal development in animal studies using 4x the exposure in humans at the recommended dose.   + A Pregnancy Exposure Registry is available: <https://covid-pr.pregistry.com> or call 1-800-616-3791   + [NIH treatment guidelines](https://www.covid19treatmentguidelines.nih.gov/special-populations/pregnancy/) recommend against withholding COVID-19 treatments or vaccination from pregnant or lactating individuals * Lactation   + Case report data is available that describes the presence of remdesivir and its active metabolite in human milk. Data from pharmacovigilance reports did not identify adverse effects on breastfed infants from exposure. For more information, refer to the [manufacturer prescribing information](https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf).   + Non-clinical reproductive studies in animals found detectable levels of remdesivir and its metabolites in nursing pups, exposures where approximately 1% that of maternal exposures   + Additional information regarding the use of remdesivir while breastfeeding can be found in the National Library of Medicine Drugs and Lactation Database [here](https://www.ncbi.nlm.nih.gov/books/NBK556881/#:~:text=Summary%20of%20Use%20during%20Lactation&text=%5B1%2D3%5D%20Given%20this,careful%20infant%20monitoring%20during%20breastfeeding.), and from a recent review regarding available data [here](https://academic.oup.com/jac/article/77/1/24/6356837). * Providers should report any adverse events observed   + To report suspected adverse reactions, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)   **Clinical Data** Severe COVID-19 (5-day regimen)  * + Several trials have evaluated the clinical efficacy of remdesivir and are summarized by the NIH [here](https://www.covid19treatmentguidelines.nih.gov/tables/remdesivir-data/). Summarized below are the primary trials that (1) resulted in FDA approval for use, (2) provide support for the current guideline recommended duration of therapy, and (3) provide *support* for prioritizing administration within the first 7 days of symptom onset.  [ACTT-1 Trial](https://pubmed.ncbi.nlm.nih.gov/32445440/) – Randomized, double blind, placebo-controlled, phase 3 in hospitalized adult patients with confirmed SARS-CoV-2 infection and mild, moderate, or severe COVID-19  * + - Primary endpoint:       * 5 day shorter time to recovery\* (median 10 days remdesivir vs. 15 days placebo; recovery rate ratio 1.29 (95% CI, 1.12-1.49; p<0.001)       * Median time to recovery in patients with symptom onset ≤10 days (n=676) was 9 days with VEKLURY vs 15 days with placebo; recovery rate ratio: 1.37 (95% Cl, 1.14 to 1.64). Median time to recovery in patients with symptom onset >10 days (n=383) was 11 days with VEKLURY vs 15 days with placebo; recovery rate ratio: 1.20 (95% Cl, 0.94 to 1.52).       * \*Recovery defined as no longer hospitalized or hospitalized but no longer needing ongoing COVID-19 medical care     - Secondary endpoints:       * Patients that received remdesivir were 54% more likely to have improved clinical status at day 29 compared to placebo (odds ratio for improvement 1.54 (95% CI, 1.25-1.91)         + No difference in time to recovery was observed among patients on high-flow nasal cannula, non-invasive ventilation, mechanical ventilation, or ECMO at enrollment       * Median time on oxygen was reduced by 8 days with remdesivir (95% CI, -11.8 to -4.2)       * Incidence of new non-invasive ventilation or high-flow oxygen reduced with remdesivir (absolute reduction 7% (95% CI -14 to -1)) and incidence of new mechanical ventilation or ECMO reduced (absolute risk reduction 10% (95% CI -15 to -4)).       * For patients on low-flow O2, mortality rates at day 29 where reduced by 70%; HR:0.30 (95%CI, 0.14 to 0.64).       * No significant difference in mortality at day 29 (11% remdesivir vs. 15% placebo; hazard ratio 0.73 (95% CI 0.52 – 1.03)     - **Key Findings: Remdesivir shortens time to recovery, reduces time on oxygen supplementation, reduces risk of progression to more severe disease, and is associated with improved clinical status at day 29 compared to placebo. However, there was no survival benefit demonstrated overall and no difference in time to recovery in those requiring high flow oxygen, mechanical ventilation or ECMO.**  [GS-US-540-5773 Trial](https://pubmed.ncbi.nlm.nih.gov/32459919/) – Multinational, open-label, randomized controlled trial of 10 days or 5 days of remdesivir Compared with Standard of Care in Hospitalized patients with Severe COVID-19  * + - Primary endpoint       * Clinical improvement (by 2 points on a 7 point ordinal scale) by day 14: 65% in the 5-day and 54% in the 10-day arms, p=0.14     - Secondary endpoints       * Time to recovery: 10 days in the 5-day group and 11 days in the 10-day group (baseline adjusted difference 0.81 (95% CI 0.64-1.04))       * Mortality: 8% in the 5-day group vs. 11% in the 10-day group     - **Key finding: no significant difference in outcomes with a 5-day course versus a 10-day course among those with severe COVID-19 not requiring mechanical ventilation or ECMO** (*patients with mechanical ventilation or ECMO were excluded from the trial*)  [DisCoVeRy Trial](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00485-0/fulltext) - Open-Label, adaptive randomized controlled trial of remdesivir in hospitalized patients with moderate or severe COVID-19 compared to standard of care  * + - Primary endpoint       * Clinical status day 15: no difference between remdesivir or standard of care (odds ratio 0.98, 95% CI 0.77-1.25, p=0.85)     - Secondary endpoint       * No significant difference in mortality between groups at day 29 (8% remdesivir vs. 9% standard of care)     - Median time to from symptom onset to initiation of therapy was 9 days (range 7-12 days)     - **Key Finding: No clinical benefit with remdesivir if given >7 days from symptom onset**   + [**SOLIDARITY (WHO) Trial**](https://www.thelancet.com/action/showPdf?pii=S0140-6736%2822%2900519-0) **– Open-label, adaptive randomized controlled trial evaluating remdesivir use in patients hospitalized with COVID-19**   + Primary endpoint:   + In-hospital mortality: 14.5% remdesivir versus 15.6% control; mortality rate ratio 0.91 (95% CI 0.82-1.02, p=0.12)   + Of those that were mechanically ventilated: 42.1% remdesivir versus 38.6% control; mortality rate ratio 1.13 (95% CI 0.89-1.42, p=0.32)   + Of those not ventilated but on oxygen: 14.6% remdesivir versus 16.3% control; mortality rate ratio 0.87 (95% CI 0.76-0.99, p=0.03)   + Secondary endpoints:   + Progression to ventilation if not already ventilated: 14.1% remdesivir versus 15.7% control; RR 0.88 (95% CI 0.77-1.0, p=0.04)   + Time-to-discharge from hospital: remdesivir delayed discharge by 1 day (during 10 day treatment period).   + No data provided on time from symptom onset to study enrollment   + **Key finding: No benefit to the use of remdesivir in patients mechanically ventilated at baseline, small but significant effect on reducing mortality and progression to mechanical ventilation among hospitalized patients who require oxygen supplementation at baseline.**  Mild-to-moderate COVID-19 (3-day regimen)[PINETREE Trial](https://pubmed.ncbi.nlm.nih.gov/34937145/) - Double-Blind, Placebo-Controlled Trial of Remdesivir for 3 Days in Unvaccinated, Non-hospitalized Patients with COVID-19 Who Were at High Risk of Disease Progression  * + - Primary endpoint       * Composite of hospitalizations related to COVID-19 and death: 0.7% remdesivir vs. 5.3% placebo (hazard ratio 0.13 (95% CI 0.03-0.59; p=0.008))     - Secondary endpoints       * Composite of COVID-19 related medically attended visits or deaths from any cause at day 28: 1.6% remdesivir vs. 8.3% placebo (hazard ratio 0.19 (95% CI 0.07-0.56)       * COVID-19 related hospitalization by day 28: 1.8% remdesivir vs. 6.4% placebo (hazard ratio 0.28 (95% CI 0.10-0.75))       * Alleviation of baseline COVID-19 symptoms by day 14: 36.1% remdesivir vs. 20% placebo (rate ratio 1.92 (95% CI 1.26-2.94))       * Time weighted average change in viral load from baseline to day 7: -1.24 remdesivir vs. -1.14 placebo (least squares mean 0.07 (95% CI -0.10 – 0.24))       * Zero deaths occurred in both groups     - **Key finding: a 3-day regimen of remdesivir reduced the rate of hospitalizations and death among unvaccinated patients with mild-to-moderate COVID-19 with risk factors for clinical progression** (*mean age was 50 years and the most common risk factors were hypertension, diabetes, and obesity; vaccinated patients excluded from the trial*)   **For a comprehensive summary of clinical trials evaluating remdesivir use in the treatment of COVID-19, refer to NIH COVID-19 treatment Guideline, Table 4a. Remdesivir: Selected Clinical Data:** [**https://www.covid19treatmentguidelines.nih.gov/tables/remdesivir-data/**](https://www.covid19treatmentguidelines.nih.gov/tables/remdesivir-data/)    **Additional Considerations**   * Remdesivir therapy is most effective when initiated early in the course of infection, *ideally* within the first 7 days of symptom onset (*based on the findings of the DisCoVeRy trial, note that national guidelines do not set a limitation on time from symptom onset*)   + Remdesivir targets a primary process for viral replication, when viral replication is at its peak, remdesivir effectiveness is most optimized   + Clinical trial data shows lack of clinical benefit in patients receiving therapy >7 days from symptom onset * Remdesivir is effective against current circulating SARS-CoV-2 omicron variants based on [in vitro data](https://pubmed.ncbi.nlm.nih.gov/35085683/)   + Additional information regarding COVID-19 therapeutics and effectiveness against circulating variants is available through the National Institutes of Health (NIH) National Center for Advancing Translational Sciences [OpenData Portal](https://opendata.ncats.nih.gov/variant/activity) * Remdesivir is approved for COVID-19 treatment only, it is not approved for pre- or post-exposure prophylaxis * Treatment of COVID-19 with remdesivir is not a substitute for vaccination, patients who are eligible for vaccination should be encouraged to get vaccinated against COVID-19   + CDC recommendations for COVID-19 vaccination are available [here](https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html)   **Additional Resources**   * [Remdesivir (Veklury®) Prescribing information](https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf) * [NIH COVID-19 treatment guidelines](https://www.covid19treatmentguidelines.nih.gov/tables/remdesivir-data/) * [IDSA COVID-19 treatment guidelines](https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/) * IDSA COVID-19 Real-Time Learning Network - [Remdesivir page](https://www.idsociety.org/covid-19-real-time-learning-network/therapeutics-and-interventions/remdesivir3/) * IDSA COVID-19 Real-Time Learning Network- [Remdesivir Quick Point-of-Care Reference](https://www.idsociety.org/covid-19-real-time-learning-network/therapeutics-and-interventions/remdesivir2/) |
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