Drugs (2023) 83:1215–1237
https://doi.org/10.1007/s40265-023-01926-0

ADIS DRUG EVALUATION

Remdesivir: A Review in COVID-19

Hannah A. Blair[1]

Accepted: 25 July 2023 / Published online: 17 August 2023

Abstract

Remdesivir (Veklury®), a nucleotide analogue prodrug with broad-spectrum antiviral activity, is approved for the treatment of coronavirus disease 2019 (COVID-19), the illness caused by severe acute respiratory syndrome coronavirus 2 infection. Unlike some antivirals, remdesivir has a low potential for drug-drug interactions. In the pivotal ACTT-1 trial in hospitalized patients with COVID-19, daily intravenous infusions of remdesivir significantly reduced time to recovery relative to placebo. Subsequent trials provided additional support for the efficacy of remdesivir in hospitalized patients with moderate or severe COVID-19, with a greater benefit seen in patients with minimal oxygen requirements at baseline. Clinical trials also demonstrated the efficacy of remdesivir in other patient populations, including outpatients at high risk for progression to severe COVID-19, as well as hospitalized paediatric patients. In terms of mortality, results were equivocal. However, remdesivir appeared to have a small mortality benefit in hospitalized patients who were not already being ventilated at baseline. Remdesivir was generally well tolerated in clinical trials, but pharmacovigilance data found an increased risk of hepatic, renal and cardiovascular adverse drug reactions in the real-world setting. In conclusion, remdesivir represents a useful treatment option for patients with COVID-19, particularly those who require supplemental oxygen.

Plain Language Summary

Coronavirus disease 2019 (COVID-19) was first reported in China in 2019 and quickly spread around the world. The symptoms of COVID-19 can vary from person to person, with some people having no symptoms and others becoming very unwell. Most patients with COVID-19 can treat their symptoms at home, but some patients may be admitted to hospital and/or treated with specialized medications such as remdesivir (Veklury®). Remdesivir is an antiviral medicine that can reduce the amount of virus that causes COVID-19. It is given once a day, usually for 5–10 days, as an intravenous infusion. Remdesivir has been shown to improve the recovery time in hospitalized patients with COVID-19, including children and adolescents. It may also reduce the risk of death in hospitalized patients who are not being ventilated before they start treatment. A 3-day course of remdesivir is also effective in patients whose age or underlying health puts them at high risk for becoming severely ill. The drug is generally well tolerated. Therefore, remdesivir is a useful treatment option for patients with COVID-19, especially those who require additional oxygen.

Digital Features for this Adis Drug Evaluation can be found at https://doi.org/10.6084/m9.figshare.23304182.

The manuscript was reviewed by: ***D. S.-C. Hui,*** Stanley Ho Centre for Emerging Infectious Diseases, Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China; ***J. H. Levy***, Anesthesiology, Critical Care & Surgery, Duke University School of Medicine, Durham, NC, USA; ***A. Singh***, Department of Pharmacology, All India Institute of Medical Sciences, Raipur, Chhattisgarh, India.

✉ Hannah A. Blair
demail@springer.com

[1] Springer Nature, Private Bag 65901, Mairangi Bay, Auckland 0754, New Zealand

1 Introduction

Coronavirus disease 2019 (COVID-19), the illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, first appeared in China in December 2019 as an unusual idiopathic pneumonia [1]. The global spread of COVID-19 was rapid, with the World Health Organization (WHO) declaring it a global pandemic in March 2020 [2, 3]. An urgent need to control the pandemic and ease the burden on healthcare systems, together with an ongoing improved understanding of the pathophysiology of COVID-19, led to the rapid development and authorization of numerous COVID-19 vaccines and novel therapeutics (some of which were repurposed) [4].

Remdesivir: clinical considerations in COVID-19
Antiviral drug with low potential for drug-drug interactions; administered via intravenous infusion
Improves time to recovery in hospitalized patients
May have a mortality benefit in hospitalized patients with minimal oxygen requirements
Reduces the risk of hospitalization or death in outpatients at high risk for disease progression
Generally well tolerated

COVID-19 is a highly contagious respiratory illness that spreads mainly via exposure to airborne particles and droplets [2]. The symptoms of COVID-19 vary widely, but often include fever, cough, and breathing difficulties [2]. The spectrum of its clinical presentation ranges from asymptomatic infection to severe life-threatening acute respiratory failure with multiple organ dysfunction [2, 3]. The risk of severe disease, hospitalization and death is higher in elderly patients, males, smokers, and those with certain underlying medical conditions [3]. Most patients with mild COVID-19 can safely treat their symptoms at home [4]. However, some patients with COVID-19, particularly high-risk patients, require additional treatments such as immunomodulatory agents and antiviral drugs [2].

Remdesivir (Veklury®) is a broad-spectrum antiviral drug with activity against viruses from several families, including coronaviruses [3, 5]. It was previously under development for the treatment of Ebola virus disease [3, 5]. Remdesivir is approved for the treatment of COVID-19 in multiple countries worldwide, including the USA [6] and those of the EU [7]. This article reviews the clinical efficacy and tolerability of remdesivir in this indication and summarizes its pharmacological properties.

2 Pharmacodynamic Properties of Remdesivir

2.1 Mechanism of Action

Remdesivir is a prodrug of an adenosine nucleotide analogue [6–8]. Upon distribution within host cells, remdesivir is metabolized by carboxyesterase 1 and/or cathepsin A to form a nucleoside monophosphate intermediate, which is then phosphorylated by cellular kinases to form GS-443902, a pharmacologically active nucleoside triphosphate metabolite (Sect. 3) [6]. Acting as an adenosine triphosphate (ATP) analogue, remdesivir triphosphate has favourable selectivity over the natural ATP substrate for incorporation into nascent viral RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase (also known as Nsp12) [6–8]. RNA synthesis is subsequently inhibited when remdesivir triphosphate has been incorporated into the chain and is present in the viral RNA template [6–8]. Remdesivir residues embedded in the first RNA strand used as a template may also cause inhibition during synthesis of the second RNA strand (i.e. during transcription of viral genome synthesis), suggestive of a second mechanism of action [9].

2.2 Antiviral Activity

Remdesivir has broad-spectrum antiviral activity against Ebola virus, Nipah virus, respiratory syncytial virus (RSV) and a number of coronaviruses, including Middle East respiratory syndrome coronavirus and SARS-CoV-2 [8]. In vitro, remdesivir demonstrated antiviral activity against SARS-CoV-2 infection of primary human airway epithelial cells, inhibiting SARS-CoV-2 replication with a half-maximal effective concentration (EC_{50}) of 9.9 nM after 48 h of drug exposure [6, 7]. Remdesivir also inhibited SARS-CoV-2 replication in the continuous human lung epithelial cell lines Calu-3 and A549-hACE2, with EC_{50} values of 280 nM after 72 h of exposure and 115 nM after 48 h of exposure, respectively. The antiviral activity of remdesivir was dose-dependently antagonized by chloroquine phosphate when the two drugs were co-incubated at clinically relevant concentrations in RSV-infected cells. Higher concentrations of chloroquine phosphate led to higher remdesivir EC_{50} values and reduced formation of remdesivir triphosphate. Therefore, coadministration of remdesivir and chloroquine phosphate or hydroxychloroquine sulphate is not recommended [6, 7].

The potency of remdesivir against current and emerging SARS-CoV-2 variants was similar to that against earlier lineage isolates [6, 7]. In vitro, remdesivir had antiviral activity (< 2.5-fold change) against clinical isolates belonging to the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Epsilon (B.1.429), Kappa (B.1.617.1), Lambda (C.37), Iota (B.1.526) and Zeta (P.2) variants. Remdesivir also had antiviral activity (< 0.6-fold change) against clinical isolates belonging to the Delta (B.1.617.2) and Omicron (B.1.1.529 sublineages BA.1 and BA.2) variants of concern [6, 7]. A structural genomic analysis of Nsp12 substitutions demonstrated that remdesivir retained potent in vitro antiviral activity against all recent Omicron subvariants (i.e. BA.2, BA.2.12.1, BA.4, BA.5 and BA.2.75) [10]. Mean remdesivir

EC_{50} values ranged from 24.5 nM (BA.2) to 106.0 nM (BA.5), representing 0.15- to 0.66-fold changes versus the ancestral WA1 isolate [10].

In mice infected with chimeric SARS-CoV expressing the SARS-CoV-2 RNA-dependent RNA polymerase, treatment with remdesivir significantly ($p = 0.0012$ vs vehicle) reduced lung viral load and significantly ($p \leq 0.004$ vs vehicle) improved pulmonary function [11]. Similarly, in rhesus macaques infected with SARS-CoV-2, treatment with remdesivir was associated with significantly ($p \leq 0.0069$ vs vehicle) less severe pulmonary infiltration and significantly ($p \leq 0.0004$ vs vehicle) lower clinical scores [12]. Following euthanasia, remdesivir-treated macaques had significantly ($p \leq 0.0002$ vs vehicle) reduced lung viral load and lung damage [12].

2.3 Resistance

Cell culture resistance selection data suggest that multiple amino acid substitution pathways may be involved in conferring resistance to remdesivir [6, 7]. V166A, N198S, S759A, V921I, C799F and C799R amino acid substitutions in the viral RNA-dependent RNA polymerase (Nsp12) were associated with 2.7- to 10.4-fold reductions in remdesivir susceptibility. When these mutations were individually introduced into a wild-type recombinant virus, 1.7- to 3.5-fold reduced susceptibility to remdesivir was observed. In vitro selection of remdesivir-resistant SARS-CoV-2 isolate containing the P323L substitution in the viral polymerase revealed the emergence of a single amino acid substitution at V166L [6, 7]. Recombinant SARS-CoV-2 viruses with substitutions at P323L alone [6, 7], V166L alone [13] or P323L + V166L [6, 7] exhibited 1.3- to 1.5-fold increases in remdesivir susceptibility [6, 7, 13], indicating a high in vitro barrier to remdesivir resistance [13].

Two amino acid substitutions (F476L and V553L) in the viral RNA-dependent RNA polymerase conferred 5.6-fold reduced susceptibility to remdesivir in a murine hepatitis coronavirus model [6, 7]. When these substitutions were introduced into SARS-CoV, 6-fold reduced susceptibility to remdesivir was observed, with attenuation of SARS-CoV pathogenesis in a mouse model. When introduced into a SARS-CoV-2 recombinant virus, these substitutions were associated with 2-fold reductions in susceptibility to remdesivir [6, 7].

In outpatients with COVID-19 in the PINETREE trial (Sect. 4.3), emergent amino acid substitutions in Nsp12 were observed in 7% of remdesivir recipients and 5% of placebo recipients [14]. Only one patient developed a rare Nsp12 substitution with diminished viral fitness that was associated with reduced in vitro susceptibility to remdesivir, indicating a high barrier to resistance [14]. In another study, no significant viral mutations were associated with remdesivir treatment failure in patients with severe COVID-19, except for the de novo E83D mutation, which emerged in an immunosuppressed patient after 18 days of treatment [15]. Real-world studies (Sect. 4.7) demonstrated very low levels of remdesivir resistance that were stable over time [16]. Remdesivir resistance may be overcome by using increased non-toxic concentrations of remdesivir, RNA-dependent RNA polymerase compounds with increased affinity, or alternative therapeutic targets (e.g. 3C-like-protease/Mpro/Nsp5 inhibitors) [16].

3 Pharmacokinetic Properties of Remdesivir

Following intravenous administration in healthy adults, remdesivir demonstrated linear, dose-proportional pharmacokinetics over the 3–225 mg dose range [17]. The pharmacokinetic parameters of the lyophilized and solution formulations of remdesivir were comparable. Following multiple doses of 150 mg once daily for 7 or 14 days, the pharmacokinetic profile of remdesivir was similar to that seen after single-dose administration [17]. In hospitalized patients with COVID-19, the pharmacokinetics of remdesivir and its main metabolite GS-441524 were best described by a one-compartment model [18].

Following intravenous administration of the adult dosage regimen of remdesivir in volunteers, plasma concentrations peaked at the end of infusion (regardless of dose level) and declined rapidly thereafter [7]. Peak plasma concentrations of GS-441524 were seen 1.5–2.0 h after the start of a 30-min infusion [6, 7]. Remdesivir is 88–94% bound to human plasma proteins, with a blood-to-plasma ratio of 0.68–1.0 [6, 7]. GS-441524 and GS-704277 have human plasma protein binding rates of 2% and 1%, respectively [6].

Remdesivir undergoes extensive metabolism to form GS-443902, the pharmacologically active nucleoside analogue triphosphate (Sect. 2.1) [7, 17]. Remdesivir initially undergoes hydrolysis by esterases, forming the intermediate metabolite GS-704277 [7, 17]. Carboxylesterase 1 and cathepsin A are responsible for 80% and 10% of remdesivir metabolism, respectively [6, 7], with CYP3A being responsible for the remaining 10% [6]. Phosphoramidate cleavage of GS-704277 and further phosphorylation of the resultant nucleoside analogue monophosphate produces GS-443902 [7, 17]. Dephosphorylation of all phosphorylated metabolites can produce the nucleoside analogue GS-441524 [7, 17].

GS-441524 is eliminated primarily via the kidneys (glomerular filtration and active tubular secretion) [6, 7]. Following intravenous administration of a single 150 mg radiolabeled dose of remdesivir, ≈ 74% of the dose was recovered in urine and 18% in the faeces [7]. Almost half of the dose

recovered in urine was GS-441524, with 10% recovered as remdesivir. The median terminal half-lives of remdesivir and GS-441524 were ≈ 1 h and ≈ 27 h, respectively [6, 7]. In population pharmacokinetic analyses of hospitalized patients with COVID-19, remdesivir was eliminated rapidly, while GS-441524 was eliminated relatively slowly [18, 19].

3.1 Special Populations

Sex and age had no effect on the pharmacokinetics of remdesivir and its metabolites (GS-704277 and GS-441524) [6, 7]. Pharmacokinetic parameters in paediatric patients were similar to those in adults [6]. In paediatric patients in the CARAVAN trial (Sect. 4.4), pharmacokinetic results supported the use of a flat-dose regimen for patients weighing ≥ 40 kg and a weight-based regimen for those weighing between 3 and < 40 kg [20]. Although age is an independent predictor of GS-441524 exposure [21], with modest increases in GS-441524 exposure seen in patients aged ≥ 60 years [7], no dose adjustment is required in patients aged ≥ 65 years [6, 7]. In a prospective, open-label, phase IV opportunistic study (IMPAACT 2032), remdesivir, GS-704277 and GS-441524 exposures were generally comparable between pregnant and non-pregnant women [22].

The pharmacokinetics of remdesivir and GS-441524 have not been evaluated in patients with hepatic impairment [6, 7]. Kidney function and the timing of remdesivir administration around dialysis had no effect on the pharmacokinetics of remdesivir [6, 7]. The clearance of GS-441524 is dependent on the estimated glomerular filtration rate (eGFR) [18, 19, 21]. Although exposures of GS-441524 and GS-704277 were increased in patients with renal impairment relative to those with normal renal function, this finding was not clinically significant [6, 7]. Based on pharmacokinetic analyses in healthy subjects with mild (eGFR 60–89 mL/min/1.73 m^2), moderate (eGFR 30–59 mL/min/1.73 m^2) or severe (eGFR 15–29 mL/min/1.73 m^2) renal impairment, or with kidney failure or end-stage renal disease (ESRD; eGFR < 15 mL/min/1.73 m^2) [6, 7] and in COVID-19 patients with severely impaired kidney function (eGFR < 30 mL/min/1.73 m^2) in the REDPINE trial (Sect. 4.5) [23], no dose adjustment is required for patients with renal impairment, including those on dialysis [6, 7].

3.2 Potential Drug Interactions

No clinical drug–drug interaction studies have been performed with remdesivir [6]. However, based on in vitro data, phase I trials in healthy volunteers, and pharmacokinetic modeling, remdesivir has a low potential for clinically relevant drug–drug interactions [24]. Due to the rapid clearance of the drug, no clinically relevant transporter-mediated drug-drug interactions are expected [25]. In vitro, remdesivir is a substrate for CYP3A4, OATP1B1 and P-glycoprotein transporters, and esterases in plasma and tissue [6, 7]. The metabolite GS-704277 is a substrate for OATP1B1 and OATP1B3 [7]. In vitro, remdesivir is an inhibitor of CYP3A4, UGT1A1, MATE1, OAT3, OCT1, OATP1B1 and OATP1B3. Coadministration of remdesivir with sensitive substrates of these enzymes and/or transporters should be considered with caution. Due to its rapid clearance after intravenous administration, remdesivir is unlikely to have a clinically significant interaction with the CYP3A4 substrate dexamethasone. Because remdesivir is an inducer of CYP1A2 and potentially CYP3A4 in vitro, CYP1A2 or CYP3A4 substrates with narrow therapeutic indices may be less effective if coadministered with remdesivir [7]. Consult local prescribing information for further details regarding potential drug interactions.

4 Therapeutic Efficacy of Remdesivir

The efficacy of remdesivir for the treatment of COVID-19 was demonstrated in a large number of key clinical trials, including in hospitalized patients (Sect. 4.1), as combination therapy (Sect. 4.2), in outpatients at high risk for disease progression (Sect. 4.3), in paediatric patients (Sect. 4.4) and in renally impaired patients (Sect. 4.5). Compassionate use of remdesivir (Sect. 4.6) and the effectiveness of remdesivir in the real-world setting (Sect. 4.7) are also discussed.

4.1 In Hospitalized Patients

4.1.1 ACTT-1

The pivotal, randomized, double-blind, multinational, phase III ACTT-1 trial enrolled hospitalized adults (≥ 18 years of age) with COVID-19 [26]. All patients met one of the following criteria suggestive of lower respiratory tract infection: radiographic infiltrates by imaging study; peripheral oxygen saturation ≤ 94% on room air; or requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). At baseline, the mean age of patients was 59 years and 55% of patients had ≥ 2 co-existing conditions. Patients were randomized 1:1 to receive remdesivir ($n = 541$) or placebo ($n = 521$). Randomization was stratified by study site and disease severity at enrolment. Severe disease was defined as requiring mechanical ventilation or supplemental oxygen, oxygen saturation ≤ 94% on ambient air, or tachypnoea (i.e. respiratory rate of ≥ 24 breaths/min). Remdesivir was administered intravenously as a 200 mg loading dose on day 1, then 100 mg on days 2 through 10 or until hospital discharge or death. All patients received standard supportive care. The primary

endpoint was time to recovery, defined as the first day, during the 28 days after enrolment, on which a patient met the criteria for category 1, 2 or 3 on an 8-point ordinal scale ranging from 1 (not hospitalized and no limitations of activities) to 8 (death) [26].

Remdesivir significantly reduced time to recovery relative to placebo in hospitalized adults with COVID-19 (Table 1) [26]. The median time to recovery was 10 days with remdesivir and 15 days with placebo; the overall rate ratio (RR) for recovery was 1.29 (95% CI 1.12–1.49). Among patients with severe disease ($n = 957$), the median time to recovery was 11 days with remdesivir and 18 days with placebo (RR 1.31; 95% CI 1.12–1.52). Among patients requiring supplemental (low-flow) oxygen at enrolment (i.e. baseline ordinal score of 5), the median time to recovery was 7 days with remdesivir and 9 days with placebo (RR 1.45; 95% CI 1.18–1.79). Among patients requiring mechanical ventilation or ECMO at enrolment (i.e. baseline ordinal score of 7), the median time to recovery was 29 days with remdesivir and 28 days with placebo (RR 0.98; 95% CI 0.70–1.36). After adjusting for baseline ordinal score, the RR for recovery was 1.26 (95% CI 1.09–1.46). The RR for recovery was 1.37 (95% CI 1.14–1.64) among patients who began treatment during the first 10 days of symptom onset, and 1.20 (95% CI 0.94–1.52) among patients who began treatment > 10 days after symptom onset [26].

Remdesivir recipients were more likely than placebo recipients to have clinical improvement at day 15 (Table 1) [26]. Most secondary endpoints, including Kaplan-Meier estimates of mortality by day 15 and day 29, time to clinical improvement, and median duration of hospitalization, also favoured remdesivir over placebo (Table 1). Among the subgroup of patients requiring low-flow oxygen (i.e. baseline ordinal score of 5), remdesivir was associated with a 70% reduction in mortality risk compared with placebo [4 vs 13%; hazard ratio (HR) 0.30; 95% CI 0.14–0.64]. Remdesivir was also associated with fewer days of oxygen use among 913 patients receiving oxygen at baseline (median 13 vs 21 days with placebo) and shorter duration of mechanical ventilation or ECMO among 285 patients receiving these interventions at baseline (median 17 vs 20 days vs placebo) [26]. Remdesivir did not significantly reduce the amount of detectable SARS-CoV-2 RNA in nasopharyngeal swabs compared with placebo [6].

Table 1 Efficacy of remdesivir in hospitalized patients with COVID-19 in the phase III ACTT-1 trial [26]

Endpoints (ITT population)	REM[a] ($n = 541$)	PL ($n = 521$)	RR/OR/HR (95% CI)
Median time to recovery[b] (days)	10*	15	RR 1.29 (1.12–1.49)
Clinical status at day 15 (% of pts)			OR 1.5 (1.2–1.9)
1: Not hospitalized and no limitations of activities	29	22	
2: Not hospitalized, with limitation of activities, home O_2 requirement or both	22	20	
3: Hospitalized, not requiring supplemental O_2 or ongoing medical care	3	2	
4: Hospitalized, not requiring supplemental O_2 but requiring ongoing medical care	7	6	
5: Hospitalized, requiring supplemental O_2	11	12	
6: Hospitalized, requiring NIV or high-flow O_2	5	5	
7: Hospitalized, receiving IMV or ECMO	18	23	
8: Death	6	11	
Median time to clinical improvement (days)			
Improvement of 1 point on an 8-point ordinal scale	7	9	RR 1.23 (1.08–1.41)
Improvement of 2 points on an 8-point ordinal scale	11	14	RR 1.29 (1.12–1.48)
Discharge or NEWS ≤ 2 for 24 h	8	12	HR 1.27 (1.10–1.46)
Median duration of initial hospitalization (days)	12	17	
Rehospitalization (% of pts)	5	3	
Kaplan–Meier estimate of mortality (%)			
Day 15	7	12	HR 0.55 (0.36–0.83)
Day 29	11	15	HR 0.73 (0.52–1.03)

ECMO extracorporeal membrane oxygenation, *HR* hazard ratio, *IMV* invasive mechanical ventilation, *ITT* intention-to-treat, *NEWS* National Early Warning Score, *NIV* non-invasive ventilation, *O_2* oxygen, *OR* odds ratio, *PL* placebo, *pt(s)* patient(s), *REM* remdesivir, *RR* rate ratio

*$p < 0.001$ vs PL

[a]Intravenous infusion of 200 mg on day 1 and 100 mg on subsequent days

[b]Primary endpoint, defined as the first day, during the 28 days after enrolment, on which a pt met the criteria for category 1, 2 or 3 on an 8-point ordinal scale

In a post hoc analysis ($n = 1051$), remdesivir significantly reduced the risk of progression to invasive mechanical ventilation (IMV) or death (HR 0.67; 95% CI 0.52–0.87; $p = 0.0023$) [27]. Similar results were seen in patients requiring supplemental oxygen at baseline (HR 0.45; 95% CI 0.29–0.71; $p = 0003$) and patients in the 'high risk' quartile (HR 0.59; 95% CI 0.39–0.87; $p = 0.009$) [27]. In another secondary analysis ($n = 1051$), remdesivir reduced clinical deterioration (HR 0.73; 95% CI 0.59–0.91) and increased clinical improvement (HR 1.22; 95% CI 1.03–1.39) relative to baseline [28]. Similar reductions in the rate of clinical deterioration were seen among patients receiving non-intensive care unit (ICU) respiratory therapies (i.e. room air or low-flow oxygen; HR 0.74; 95% CI 0.57–0.94) and those receiving ICU respiratory therapies [i.e. mechanical ventilation, high-flow oxygen and non-invasive ventilation (NIV); HR 0.73; 95% CI 0.53–1.00] at baseline [28]. A small substudy of ACTT-1 ($n = 19$) did not identify any large differences between remdesivir and placebo in antibody or cytokine responses [29].

4.1.2 SIMPLE-severe

The randomized, open-label, multinational, phase III SIMPLE-severe trial enrolled adults and adolescents ≥ 12 years of age hospitalized with severe COVID-19 [30]. They had confirmed SARS-CoV-2 infection, radiographic evidence of pulmonary infiltrates, and either oxygen saturation ≤ 94% on room air or receipt of supplemental oxygen. Patients were randomized 1:1 to receive intravenous remdesivir (200 mg on day 1 and 100 mg once daily on subsequent days) for either 5 days ($n = 202$) or 10 days ($n = 200$). All patients continued to receive supportive therapy throughout the trial. Baseline demographic characteristics were similar in both treatment groups; however, patients in the 10-day group had significantly ($p = 0.02$) worse clinical status at baseline than those in the 5-day group. Comorbid diagnoses included hypertension (50%), diabetes (23%), hyperlipidaemia (22%) and asthma (12%). The primary endpoint was clinical status on day 14, assessed on a 7-point ordinal scale ranging from 1 (death) to 7 (not hospitalized) [30].

There was no significant difference in clinical status between a 5-day course and a 10-day course of remdesivir in hospitalized patients with severe COVID-19 [30]. After adjusting for imbalances in baseline clinical status, no significant between-group difference was seen with respect to distribution of clinical status at day 14 ($p = 0.14$; Table 2). The proportions of patients achieving clinical improvement or recovery at various timepoints (from day 5 to day 14) are presented in Table 2. The median time to clinical improvement was 10 days in the 5-day group and 11 days in the 10-day group. Similar results were seen for median time to recovery (10 vs 11 days) and median time to modified recovery (9 vs 10 days). The proportions of patients who died (8 vs 11%) or were discharged from hospital (60 vs 52%) were numerically lower in the 5-day group than in the 10-day group. Among patients requiring mechanical ventilation or ECMO, the mortality rate was 40% in the 5-day group and 17% in the 10-day group. In a post hoc analysis, treatment with remdesivir beyond 5 days did not improve outcomes in patients who were receiving NIV or high-flow oxygen, receiving low-flow oxygen, or breathing room air [30].

In comparative analyses of data from SIMPLE-severe and a real-world, retrospective, longitudinal cohort study (Sect. 4.7), remdesivir was associated with significantly higher recovery rates and lower mortality rates than standard of care (SOC) in patients with severe COVID-19 [31–33]. Inclusion criteria were similar in both studies [31]. An interim analysis was conducted in 312 patients in the remdesivir cohort and 818 patients in the SOC (non-remdesivir) cohort. The primary endpoint of this analysis was recovery on day 14, defined as improvement on a 7-point ordinal scale from a baseline score of 2–4 to a score of 5–7, from a baseline score of 5 to a score of 6 or 7, or from a baseline score of 6 to a score of 7. At day 14, the recovery rate was 74% with remdesivir versus 59% with SOC [adjusted odds ratio (OR) 2.03; 95% CI 1.34–3.08; $p < 0.001$] [31]. Similar results were seen in the final analysis of 368 remdesivir recipients and 1399 SOC recipients (65 vs 57%; OR 1.49; 95% CI 1.16–1.90; $p = 0.002$) [32]. In a subsequent propensity score weighted analysis ($n = 1974$ patients in the remdesivir cohort and 1426 patients in the SOC cohort), remdesivir reduced the risk of mortality by 54% compared with SOC (13 vs 26%; HR 0.46; 95% CI 0.39–0.54; $p < 0.001$) [33]. Remdesivir was also associated with a significantly greater likelihood of hospital discharge by day 28, both overall (70 vs 53% with SOC; HR 1.16; 95% CI 1.06–1.27; $p = 0.001$) and after 10 days of treatment (56 vs 40%; HR 1.64; 95% CI 1.43–1.87; $p < 0.001$) [33].

4.1.3 CAP-China Remdesivir 2

A randomized, double-blind, multicentre, phase III trial conducted in China enrolled patients aged ≥ 18 years who were hospitalized with severe COVID-19 [34]. All patients had confirmed SARS-CoV-2 infection, radiologically confirmed pneumonia, and either oxygen saturation of ≤ 94% on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of ≤ 300 mm Hg. They were randomized 2:1 to receive remdesivir ($n = 158$) or placebo ($n = 79$) for 10 days. Remdesivir was administered as a single intravenous infusion of 200 mg on day 1 and 100 mg on days 2–10. The primary endpoint was time to clinical

Table 2 Efficacy of remdesivir in hospitalized patients with moderate or severe COVID-19 in the phase III SIMPLE trials

Endpoints	SIMPLE-severe [30]		SIMPLE-moderate [35]		
	5-day REM[a] (*n* = 200)	10-day REM[a] (*n* = 197)	5-day REM[a] (*n* = 191)	10-day REM[a] (*n* = 193)	SOC (*n* = 200)
Clinical status at day 11 [35] or 14 [30][b] (% of pts)					
1: Death	8	11	0	1	2
2: Hospitalized, requiring IMV or ECMO	8	17	0	1	2
3: Hospitalized, requiring NIV or high-flow O_2	4	5	3	0	4
4: Hospitalized, requiring low-flow supplemental O_2	10	7	4	6	6
5: Hospitalized, not requiring supplemental O_2 but requiring ongoing medical care	6	7	20	23	23
6: Hospitalized, not requiring supplemental O_2 or ongoing medical care	4	2	4	5	4
7: Not hospitalized	60	52	70	65	60
Clinical improvement[c] (% of pts)					
Day 5	16	15	32	37	33
Day 7	36	27	56	48	47
Day 11	58	49	70	65	61
Day 14	64	54	76	77	68
Day 28	NR	NR	90	90	83
Recovery[d] (% of pts)					
Day 5	16	14	35	38	36
Day 7	36	26	60	49	51
Day 11	58	49	74	68	64
Day 14	64	54	80	79	73
Day 28	NR	NR	92	92	85

Efficacy was assessed in randomized pts who received ≥ 1 dose of REM (or for the SOC group, had the day-1 visit)

BL baseline, *ECMO* extracorporeal membrane oxygenation, *IMV* invasive mechanical ventilation, *NIV* non-invasive ventilation, *NR* not reported, O_2 oxygen, *pts* patients, *REM* remdesivir, *SOC* standard of care

[a]Intravenous infusion of 200 mg on day 1 and 100 mg on subsequent days

[b]Primary endpoint, measured on a 7-point ordinal scale

[c]Defined as improvement of ≥ 2 points from BL on a 7-point ordinal scale

[d]Defined as improvement from a BL score of 2–5 to a score of 6–7 [30, 35] or from a BL score of 6 to a score of 7 [35]

improvement up to day 28, defined as the time from randomization to the point of a decline of two levels on a 6-point ordinal scale of clinical status from 1 (discharged) to 6 (death) or discharged alive from hospital, whichever came first. The trial was terminated before attaining the prespecified sample size ($n \approx 453$); subsequently, the statistical power was reduced from 80 to 58% [34].

A 10-day course of remdesivir was not associated with a significant clinical benefit in hospitalized adults with severe COVID-19 [34]. Time to clinical improvement was not significantly different between remdesivir and placebo (median 21 vs 23 days; HR 1.23; 95% CI 0.87–1.75). However, among patients with symptom duration of ≤ 10 days, patients treated with remdesivir had a numerically faster time to clinical improvement than those receiving placebo (median 18 vs 23 days; HR 1.52; 95% CI 0.95–2.43) [34].

4.1.4 SIMPLE-moderate

The randomized, open-label, multinational, phase III SIMPLE-moderate trial enrolled adults and adolescents ≥ 12 years of age who were hospitalized with confirmed SARS-CoV-2 infection and moderate COVID-19 pneumonia (defined as radiographic evidence of pulmonary infiltrates and oxygen saturation > 94% on room air) [35]. Patients were randomized 1:1:1 to receive remdesivir for up to 5 days ($n = 199$), remdesivir for up to 10 days ($n = 197$) or SOC ($n = 200$). Patients in the remdesivir groups received remdesivir 200 mg on day 1 and 100 mg on subsequent days, as an intravenous infusion over 30–60 min. At baseline, the median age of patients was 57 years, and comorbid diagnoses included cardiovascular disease (56%), hypertension (42%), diabetes (40%) and asthma (14%). The primary

endpoint was clinical status on day 11, as measured on a 7-point ordinal scale ranging from 1 (death) to 7 (not hospitalized) [35].

Hospitalized patients with moderate COVID-19 receiving a 5-day course of remdesivir were significantly more likely to have a better clinical status on day 11 than those receiving SOC (OR 1.65; 95% CI 1.09–2.48; $p = 0.02$); the difference between patients receiving a 10-day course of remdesivir and those receiving SOC was not statistically significant ($p = 0.18$; Table 2) [35]. Similar results were seen in post hoc sensitivity analyses of the primary endpoint adjusting for day 1 clinical status score, symptom duration, imputing patients with missing status as dead, and using the intention-to-treat population. The proportions of patients achieving clinical improvement or recovery at various timepoints (from day 5 to day 28) are presented in Table 2. No significant differences were seen between the 5-day or 10-day remdesivir groups and SOC for time to clinical improvement, time to recovery, time to modified recovery, time to discontinuation of oxygen support (all prespecified exploratory endpoints), duration of oxygen therapy, duration of hospitalization, and all-cause mortality at day 28 [35].

4.1.5 WHO SOLIDARITY Programme

The randomized, open-label, multinational WHO SOLIDARITY trial enrolled adults (≥ 18 years of age) hospitalized with COVID-19 [36]. Under the initial study protocol, patients were randomized to receive no trial drug or one of four trial drug regimens: intravenous remdesivir (200 mg on day 0, then 100 mg on days 1–9), oral lopinavir/ritonavir (400/100 mg twice daily for 14 days), interferon-β-1a (3 doses of 44 µg subcutaneously over 6 days or 10 µg intravenously once daily for 6 days) or oral hydroxychloroquine (800 mg at 0 h, 800 mg at 6 h and, starting at 12 h, 400 mg twice daily for 10 days). All patients received SOC. The lopinavir/ritonavir, interferon-β-1a and hydroxychloroquine regimens were subsequently discontinued for futility. The primary endpoint was in-hospital mortality [36].

Remdesivir, lopinavir/ritonavir, interferon-β-1a and hydroxychloroquine had little or no effect on mortality in hospitalized patients with COVID-19 [36]. An interim analysis ($n = 11{,}330$) reported a total of 1253 deaths (median day of death, day 8). Overall, Kaplan-Meier 28-day mortality was 12% (39% in patients who were already ventilated at baseline and 10% otherwise). For each pairwise comparison of a trial drug and its control (i.e. SOC alone), mortality rates were 11 vs 11% for remdesivir (RR 0.95; 95% CI 0.81–1.11), 11 vs 11% for lopinavir/ritonavir (RR 1.00; 95% CI 0.79–1.25), 12 vs 11% for interferon-β-1a (RR 1.16; 95% CI 0.96–1.39) and 11 vs 9% for hydroxychloroquine (RR 1.19; 95% CI 0.89–1.59). None of the trial drugs had any definite effect on mortality, and none reduced initiation of ventilation or duration of hospitalization [36].

Final results of WHO SOLIDARITY ($n = 14{,}304$) demonstrated that remdesivir may protect against death or progression to ventilation in hospitalized patients with COVID-19 who are not already being ventilated at baseline [37]. A total of 8275 patients were randomized to either remdesivir ($n = 4146$) or its control ($n = 4129$). The overall mortality rate was 15% with remdesivir plus SOC and 16% with SOC alone (RR 0.91; 95% CI 0.82–1.02). Among patients who were already ventilated, the mortality rate was 42% with remdesivir plus SOC and 39% with SOC alone (RR 1.13; 95% CI 0.89–1.42). Of those not ventilated but on oxygen, 15% of remdesivir plus SOC recipients died compared with 16% of SOC recipients (RR 0.87; 95% CI 0.76–0.99; $p = 0.03$). Among other hospitalized patients, significantly fewer remdesivir plus SOC than SOC recipients died (12 vs 14%; RR 0.86; 95% CI 0.76–0.98; $p = 0.02$) and progressed to ventilation (14 vs 16%; RR 0.88; 95% CI 0.77–1.00; $p = 0.04$). The composite endpoint of death or progression to ventilation occurred in 20% of patients receiving remdesivir plus SOC versus 23% of those receiving SOC alone (RR 0.84; 95% CI 0.75–0.93; $p = 0.001$) [37].

4.1.5.1 DisCoVeRy The randomized, open-label, multinational, phase III DisCoVeRy trial, a European substudy of WHO SOLIDARITY, enrolled adults (≥ 18 years of age) hospitalized with COVID-19 who were in need of oxygen or ventilator support [38, 39]. All patients had confirmed SARS-CoV-2 infection and presented with at least one of the following: evidence of rales or crackles on clinical examination and oxygen saturation of ≤ 94% on room air; or requirement of supplemental oxygen, high-flow oxygen, NIV or mechanical ventilation. Patients were randomized 1:1 to receive remdesivir plus SOC ($n = 420$) or SOC alone ($n = 423$). Randomization was stratified by disease severity and European administrative region. Remdesivir was administered as an intravenous infusion of 200 mg on day 1, then 100 mg daily for 10 days. At baseline, the median age of patients was 64 years, and the most common coexisting conditions were obesity (34%), chronic cardiac disease (28%) and diabetes (27%). The primary endpoint was clinical status at day 15, as measured on a 7-point ordinal scale from 1 (not hospitalized, no limitation on activities) to 7 (death) [38, 39].

Remdesivir plus SOC had no clinical benefit in hospitalized patients with COVID-19 who required oxygen support [38]. There was no significant difference between remdesivir plus SOC and SOC alone in the distribution of the 7-point ordinal scale at day 15 (OR 1.02; 95% CI 0.62–1.70) or at day 29 (OR 1.11; 95% CI 0.87–1.43). No significant between-group differences were observed for any other secondary endpoints, including time to clinical improvement,

change from baseline in National Early Warning Score (NEWS)-2, time to hospital discharge, duration of hospitalization, time to new mechanical ventilation, ECMO or death, and in-hospital mortality [38]. However, remdesivir demonstrated modest antiviral activity, reducing viral production 2-fold and time to viral clearance by 0.7 days compared with SOC [40]. Among patients with a high viral load (≥ 3.5 $\log_{10}$ copies/10^4 cells) at baseline, remdesivir reduced viral production 5-fold and reduced time to viral clearance by 2.4 days versus SOC [40].

4.1.5.2 CATCO The randomized, open-label, multicentre, phase III CATCO trial, a Canadian substudy of WHO SOLIDARITY, enrolled adults (≥ 18 years of age) hospitalized with COVID-19 [41]. All patients had confirmed SARS-CoV-2 infection. They were randomized to receive intravenous remdesivir (200 mg on day 0 then 100 mg on days 1–9) plus SOC ($n = 634$) or SOC alone ($n = 648$). At baseline, 55% of patients were on low-flow oxygen and 21% were in the ICU. In addition to the primary endpoint of WHO SOLIDARITY (in-hospital mortality), additional prespecified endpoints for CATCO included oxygen-free and ventilator-free days at day 28, and clinical severity of illness, as assessed on the WHO ordinal scale from 0 (no illness) to 10 (death) [41].

Remdesivir plus SOC reduced the need for mechanical ventilation in hospitalized patients with COVID-19 [41]. At day 28, mean oxygen-free and ventilator-free days were 15.9 and 21.4 with remdesivir plus SOC versus 14.2 and 19.5 with SOC alone. Patients receiving remdesivir plus SOC had a 17% lower risk of death than patients receiving SOC alone (19 vs 23%; relative risk 0.83; 95% CI 0.67–1.03). Similar results were seen for 60-day mortality (25 vs 28%; relative risk 0.88; 95% CI 0.72–1.07). The proportion of patients requiring new mechanical ventilation was 8% in the remdesivir plus SOC group and 15% with SOC alone (relative risk 0.53; 95% CI 0.38–0.75). Duration of hospitalization was not significantly different between treatment groups [41].

4.1.5.3 NOR-SOLIDARITY The randomized, multicentre, phase II/III NOR-SOLIDARITY trial, a Norwegian substudy of WHO SOLIDARITY, enrolled adults (≥ 18 years of age) hospitalized with COVID-19 [42]. All patients had confirmed SARS-CoV-2 infection. Of the 181 randomized patients, 87 were assigned to receive SOC and 94 to receive either remdesivir ($n = 42$) or hydroxychloroquine ($n = 52$), with an SOC group matched to each treatment group. Remdesivir was administered as an intravenous infusion of 200 mg on day 1, then 100 mg daily up to 9 days. Hydroxychloroquine was administered orally, 800 mg twice daily on day 1, then 400 mg twice daily up to 9 days. The mean age at baseline was 60 years, and the most common comorbid conditions were ever smoking (39%), hypertension (31%) and obesity (27%). In addition to the primary endpoint of WHO SOLIDARITY (in-hospital mortality), study-specific endpoints for NOR-SOLIDARITY included viral clearance, as assessed by SARS-CoV-2 polymerase chain reaction in oropharyngeal specimens, and respiratory failure, assessed by the ratio of arterial oxygen partial pressure to fractional inspired oxygen (Pa_{O2}/Fi_{O2} ratio) and inflammatory variables [42].

Remdesivir and hydroxychloroquine had no antiviral activity in hospitalized patients with COVID-19 [42]. During the first week of treatment, remdesivir, hydroxychloroquine and SOC were associated with similar reductions in SARS-CoV-2 oropharyngeal viral load and similar increases in Pa_{O2}/Fi_{O2} ratio. Remdesivir and hydroxychloroquine had no marked or consistent effect on inflammatory variables (e.g. C-reactive protein, ferritin, lactate dehydrogenase, procalcitonin). There were no significant differences between treatment groups in terms of in-hospital mortality, rate of ICU admission, use of mechanical ventilation, time to receipt of mechanical ventilation, duration of ICU stay, and duration of mechanical ventilation [42].

4.2 As Combination Therapy

4.2.1 ACTT Trials

The randomized, double-blind, multinational, phase III ACTT-2 and ACTT-3 trials enrolled hospitalized adults (≥ 18 years of age) with COVID-19 [43, 44]. All patients met one of the following criteria suggestive of lower respiratory tract infection: radiographic infiltrates by imaging study; peripheral oxygen saturation ≤ 94% on room air; or requiring supplemental oxygen, mechanical ventilation or ECMO. Across both trials, the mean age of patients was 55–58 years and 57–68% of patients had ≥ 2 coexisting conditions [43, 44]. Patients were randomized 1:1 to receive remdesivir plus baricitinib ($n = 515$) or remdesivir plus placebo ($n = 518$) in ACTT-2 [43] and remdesivir plus interferon-β-1a ($n = 487$) or remdesivir plus placebo ($n = 482$) in ACTT-3 [44].

Randomization was stratified by study site and disease severity at enrolment [43, 44]. Remdesivir was administered intravenously as a 200 mg loading dose on day 1, then 100 mg for up to 9 days [44] or on days 2 through 10 or until hospital discharge or death [43]. In ACTT-2, baricitinib 4 mg/day (2 mg/day in patients with an estimated glomerular filtration rate of < 60 mL/min) was administered either orally or through a nasogastric tube for 14 days or until hospital discharge [43]. In ACTT-3, up to four doses of interferon-β-1a 44 µg were administered subcutaneously every other day [44]. All patients received standard supportive care [43, 44]. The primary endpoint of both trials was time to recovery, defined as the first day, during the

28 days after enrolment, on which a patient met the criteria for category 1, 2 or 3 on an 8-point ordinal scale ranging from 1 (not hospitalized and no limitations of activities) to 8 (death) [43, 44].

4.2.1.1 ACTT-2 Combination therapy with remdesivir plus baricitinib was superior to remdesivir alone in hospitalized adults with COVID-19 [43]. Patients receiving remdesivir plus baricitinib recovered significantly faster than those receiving remdesivir plus placebo (median 7 vs 8 days; RR 1.16; 95% CI 1.01–1.32; $p = 0.03$). Among patients requiring NIV or high-flow oxygen at enrolment (i.e. baseline ordinal score of 6), the median time to recovery was 10 days with remdesivir plus baricitinib and 18 days with remdesivir plus placebo (RR 1.51; 95% CI 1.10–2.08). Among patients requiring supplemental oxygen at enrolment (i.e. baseline ordinal score of 5), the RR for recovery was 1.17 (95% CI 0.98–1.39). Among patients receiving mechanical ventilation or ECMO at enrolment (i.e. baseline ordinal score of 7), the RR for recovery was 1.08 (95% CI 0.59–1.97) [43].

The odds of clinical improvement at day 15 were greater with remdesivir plus baricitinib than with remdesivir plus placebo (OR 1.3; 95% CI 1.0–1.6) [43]. Most secondary endpoints also favoured combination therapy, including Kaplan-Meier estimates of mortality by day 28 (5 vs 8% with remdesivir plus placebo; HR 0.65; 95% CI 0.39–1.09), median time to clinical improvement (6 vs 8 days; RR 1.21; 95% CI 1.06–1.39) and median time to discharge or a NEWS score of ≤ 2 for 24 h (6 vs 7 days; RR 1.24; 95% CI 1.07–1.44). The proportion of patients requiring new use of oxygen was 23% with remdesivir plus baricitinib versus 40% with remdesivir plus placebo; similar results were seen for the proportions of patients requiring new use of NIV or high-flow oxygen (20 vs 24%) and mechanical ventilation or ECMO (10 vs 15%). Combination therapy was associated with shorter duration of mechanical ventilation or ECMO (median 16 vs 27 days with remdesivir plus placebo). The incidence of progression to death or IMV was 12% with remdesivir plus baricitinib versus 17% with remdesivir plus placebo (RR 0.69; 95% CI 0.50–0.95) [43].

4.2.1.2 ACTT-3 Combination therapy with remdesivir plus interferon-β-1a was not superior to remdesivir alone in hospitalized adults with COVID-19 [44]. Patients in both treatment groups had a median time to recovery of 5 days (RR 0.99; 95% CI 0.87–1.13). Among patients requiring NIV or high-flow oxygen at enrolment (i.e. baseline ordinal score of 6), the RR for recovery was 0.40 (95% CI 0.22–0.75). The Kaplan-Meier estimates of mortality at 14 days (2 vs 2%; HR 0.73; 95% CI 0.30–1.83) and 28 days (5 vs 3%; HR 1.33; 95% CI 0.69–2.55) were not significantly different between treatment groups. There were also no significant between-group differences in other secondary endpoints, including the odds of clinical improvement at day 14 (OR 1.01; 95% CI 0.79–1.28), time to clinical improvement, and duration of hospitalization [44].

4.2.2 Other Trials

The randomized, double-blind, multinational, phase III REMDACTA trial enrolled hospitalized adults and adolescents ≥ 12 years of age with severe COVID-19 [45]. All patients had a positive SARS-CoV-2 test result, radiographically confirmed pneumonia, and hypoxaemia requiring supplemental oxygen. They were randomized 2:1 to receive remdesivir plus tocilizumab 8 mg/kg ($n = 434$) or remdesivir plus placebo ($n = 215$). Systemic corticosteroids were permitted (88%). The addition of tocilizumab to remdesivir did not shorten time to hospital discharge in patients with severe COVID-19 pneumonia. The median time from randomization to hospital discharge or 'ready for discharge' (primary endpoint) was 14 days with remdesivir plus tocilizumab and 14 days with remdesivir plus placebo (HR 0.97; 95% CI 0.78–1.19). At day 28, the proportion of patients discharged or 'ready for discharge' was 66% in the remdesivir plus tocilizumab group and 67% in the remdesivir plus placebo group [45].

A randomized, multicentre, phase III trial enrolled patients with severe COVID-19 who required ICU admission [46]. Patients aged 18–85 years were randomized 1:1 to receive remdesivir (5 mg/kg or 200 mg on day 1 then 2.5 mg/kg or 100 mg daily) plus tocilizumab 8 mg/kg ($n = 104$) or dexamethasone 6 mg/day ($n = 104$). All patients received a broad-spectrum antibacterial and other essential treatments. Remdesivir plus tocilizumab was more effective than dexamethasone for the treatment of severe COVID-19. The recovery rate was 74% with remdesivir plus tocilizumab and 69% with dexamethasone; corresponding mortality rates were 26% and 31%. Remdesivir plus tocilizumab was associated with significant ($p \leq 0.05$) reductions in time to clinical improvement (9 vs 14 days), NEWS-2 score at discharge (0.89 vs 1.2), lung recovery on chest CT at discharge (22 vs 12%), duration of ICU stay (8 vs 11 days) and duration of hospitalization (10 vs 15 days) compared with dexamethasone. However, a Kaplan–Meier analysis demonstrated no significant difference in survival between treatment groups [46].

4.3 In Outpatients at High Risk for Disease Progression

The randomized, double-blind, multinational, phase III PINETREE trial enrolled non-hospitalized adults and adolescents ≥ 12 years of age with COVID-19 at high risk for disease progression [47]. All patients had a confirmed

SARS-CoV-2 infection and ≥ 1 pre-existing risk factor for progression to severe COVID-19 (e.g. hypertension, cardiovascular or cerebrovascular disease, diabetes, obesity, immune compromise, CKD, chronic liver disease, current cancer, or sickle cell disease) or were ≥ 60 years of age. Patients were randomized 1:1 to receive intravenous remdesivir (200 mg on day 1 and 100 mg on days 2 and 3; $n = 279$) or placebo ($n = 283$). Randomization was stratified by residence in a skilled nursing facility (yes or no), age (< 60 or ≥ 60 years) and country (USA or outside the USA). At baseline, the mean age of patients was 50 years, and the most common co-existing conditions were diabetes (62%), obesity (55%) and hypertension (48%). Some patients received at least one infusion at home (17%) or in a skilled nursing facility (3%). The primary endpoint was a composite of hospitalization related to COVID-19 or death from any cause at day 28. The trial was terminated for administrative reasons prior to enrolment of the expected sample size ($n \approx 1264$); however, double-blinding was maintained until the data were finalized [47].

Remdesivir significantly reduced the risk of hospitalization or death in outpatients at high risk of disease progression [47]. The risk of COVID-19-related hospitalization or death from any cause by day 28 was 87% lower with remdesivir than with placebo (Table 3). Remdesivir also reduced the risk of COVID-19-related medically attended visits or death from any cause, as well as the risk of hospitalization for any cause (Table 3). No patients had died by day 28. Numerically more remdesivir than placebo recipients reported alleviation of COVID-19 symptoms by day 14 (Table 3). The time-weighted average change in detectable nasopharyngeal SARS-CoV-2 viral load from baseline to day 7 was not significantly different between the remdesivir and placebo groups (–1.24 vs –1.14 $\log_{10}$ copies/mL) [47]. In subgroup analyses, remdesivir significantly ($p < 0.001$) reduced the risk of COVID-19 hospitalization independent of stratification by time from symptom onset to infusion and by number of baseline risk factors for severe disease (including age ≥ 60 years, obesity and certain coexisting medical conditions) [48].

4.4 In Paediatric Patients

The single-arm, open-label, multinational, phase II/III CARAVAN trial enrolled hospitalized paediatric patients with COVID-19 [20, 49]. Patients aged 28 days to < 18 years and weighing ≥ 3 kg (i.e. cohorts 1–4 and 8) were included in an interim analysis ($n = 53$). All patients had a positive SARS-CoV-2 test result and were not receiving other antivirals. Remdesivir was administered as an intravenous loading dose of 200 mg or 5 mg/kg on day 1, then 100 mg or 2.5 mg/kg daily for up to 10 days. At baseline, the mean age of patients was 8 years and the median body weight was 25 kg. Comorbid diagnoses included obesity (37%), asthma (21%) and cardiac disorders (21%). The primary objectives were to evaluate safety and tolerability (Sect. 5.3) and pharmacokinetics (Sect. 3); efficacy was assessed as a secondary objective [20, 49].

Remdesivir was associated with clinical improvement in a high proportion of hospitalized paediatric patients with COVID-19 [20, 49]. Clinical improvement, defined as a ≥ 2-point increase from baseline on a 7-point ordinal scale from 1 (death) to 7 (discharged), was seen in 75% of patients at day 10 and in 85% of patients at their last assessment.

Table 3 Efficacy of remdesivir in outpatients at high risk of progression to severe COVID-19 in the phase III PINETREE trial [47]

Endpoints	REM[a] ($n = 279$)	PL ($n = 283$)	HR/RR (95% CI)
COVID-19-related hospitalization or death from any cause (% of pts)			
Day 28[b]	1*	5	HR 0.13 (0.03–0.59)
Day 14	1	5	HR 0.13 (0.03–0.59)
COVID-19-related medically attended visit or death from any cause (% of pts)			
Day 14	1	8	HR 0.10 (0.02–0.43)
Day 28	2	8	HR 0.19 (0.07–0.56)
Hospitalization for any cause by day 28 (% of pts)	2	6	HR 0.28 (0.10–0.75)
Death from any cause by day 28 (% of pts)	0	0	
Alleviation of COVID-19 symptoms[c] by day 14 (% of pts)			
Questionnaire completed before infusion on day 1	35	25	RR 1.41 (0.73–2.69)
Questionnaire completed on day 1, either before or after infusion	36	20	RR 1.92 (1.26–2.94)

HR hazard ratio, *PL* placebo, *pts* patients, *REM* remdesivir, *RR* rate ratio

*$p = 0.008$ vs PL

[a]Intravenous infusion of 200 mg on day 1 and 100 mg on days 2 and 3

[b]Primary endpoint

[c]Mild or absent symptoms on the Influenza Patient-Reported Outcome (FLU-PRO) Plus questionnaire, adapted for pts with COVID-19

Most (83%) patients were discharged alive by day 30. The median duration of hospitalization was 7 days. Only 8% of patients who were invasively ventilated at baseline required supplemental oxygen at the last available assessment [20, 49].

4.5 In Renally Impaired Patients

The randomized, double-blind, multinational, phase III REDPINE trial enrolled adults and adolescents ≥ 12 years of age with moderately and severely reduced kidney function who were hospitalized with severe COVID-19 pneumonia [50]. All patients had confirmed SARS-CoV-2 infection and oxygen saturation ≤ 94% on room air or required oxygen supplementation. They also had an eGFR of < 30 mL/min/1.73 m^2 due to chronic kidney disease (CKD) or acute kidney injury (AKI). Kidney transplant recipients with reduced allograft function were eligible. Patients were randomized 2:1 to receive intravenous remdesivir 200 mg on day 1 followed by 100 mg once daily on days 2–5 ($n = 163$) or placebo ($n = 80$), in addition to SOC. Randomization was stratified by chronic dialysis requirement, high-flow oxygen requirement and region (USA or outside the USA). The mean age of patients at baseline was 69 years; no patients aged 12–17 years were enrolled. Overall, 26% of patients had CKD, 37% had AKI and 37% had ESRD requiring chronic dialysis. The primary endpoint was a composite of all-cause mortality or IMV through day 29. Enrolment was terminated after 249 patients were randomized due to challenges with recruitment [50].

Remdesivir plus SOC did not reduce the risk of mortality in patients with moderately and severely reduced kidney function who were hospitalized with severe COVID-19 pneumonia [50]. The Kaplan-Meier estimate of all-cause mortality or IMV by day 29 was not significantly different between remdesivir and placebo (30 vs 34%; HR 0.82; 95% CI 0.50–1.32). Similar results were seen for all-cause mortality by day 29 (25 vs 29%; HR 0.83; 95% CI 0.50–1.39). There were no significant between-group differences for the primary endpoint by kidney disease status (i.e. CKD, AKI or ESRD). However, the trial was underpowered for efficacy due to insufficient enrolment [50].

4.6 Compassionate Use

Remdesivir was provided on a compassionate-use basis to several cohorts of patients hospitalized with severe COVID-19, including adults, pregnant and postpartum women, and paediatric patients [51–54]. All patients had confirmed SARS-CoV-2 infection and were receiving oxygen support or had an oxygen saturation of ≤ 94% while breathing room air. They received intravenous remdesivir for up to 10 days. Adults and paediatric patients weighing ≥ 40 kg received 200 mg on day 1, then 100 mg daily on each subsequent day [51–54], while paediatric patients weighing < 40 kg received 5 mg/kg on day 1, then 2.5 mg/kg on each subsequent day [52]. Overall, more than half of patients were receiving oxygen support, mechanical ventilation or ECMO at baseline [51–54]. Endpoints included clinical improvement, defined as live discharge from hospital and/or a ≥ 2-point improvement from baseline on a modified ordinal scale from 1 (not hospitalized) to 6 (death) [51–54], and clinical recovery, defined as hospital discharge for patients on room air and improvement to room air or discharge for all others [51, 52].

In a multinational cohort of 53 patients aged 23–82 years, the rate of clinical improvement was 68% after a median follow-up of 18 days [53]. The discharge rate was 47% and the mortality rate was 13% [53]. In another multinational cohort of 163 patients aged 23–86 years, the rate of clinical improvement was 47% after a median follow-up of 15 days [54]. The median time to clinical improvement was 24 days. A ≥ 2-point clinical improvement was achieved by 41% of patients and 30% of patients were discharged from hospital. The overall mortality rate was 20% [54].

Among pregnant women ($n = 67$) and postpartum women (i.e. those who gave birth prior to receiving their first dose of remdesivir; $n = 19$), rates of clinical improvement at day 28 were 96% and 89%, respectively [51]. For pregnant women, the clinical recovery rate was 93% and the discharge rate was 90%; for postpartum women, the respective rates were 89% and 84% [51].

In a cohort of 77 paediatric patients aged 0–17 years, the rate of clinical improvement at day 28 was 88% [52]. Clinical recovery was observed in 80% of patients requiring invasive ventilation at baseline and in 87% of patients not requiring invasive oxygen support [52].

4.7 Real-World Effectiveness

Extensive real-world experience has demonstrated the effectiveness of remdesivir for the treatment of COVID-19 [55–106]. For example, in the largest of these studies ($n \approx$ 15,000–250,000 remdesivir-treated patients), all of which were conducted in the USA, remdesivir reduced mortality [55–59, 61, 64], increased the likelihood of clinical improvement [64] and/or reduced the likelihood of readmission [60, 62, 63] in hospitalized adults with COVID-19.

A large retrospective cohort study analysed data from the PINC AI Healthcare Database (formerly Premier Healthcare Database) of hospitalized patients receiving remdesivir for the treatment of COVID-19 [55–60]. In one analysis,

164,791 patients who initiated remdesivir in the first 2 days of hospitalization were matched to 48,473 patients not receiving remdesivir [55]. Between December 2020 and April 2022, remdesivir significantly reduced mortality at 14 and 28 days, regardless of baseline oxygen requirements (all $p < 0.0001$). The 28-day mortality benefit of remdesivir was most prominent in patients receiving no supplemental oxygen (HR 0.81; 95% CI 0.74–0.89), low-flow oxygen (HR 0.79; 95% CI 0.73–0.85) or IMV/ECMO (HR 0.74; 95% CI 0.67–0.82) at baseline. Similar results were seen across all variant time periods of the pandemic (i.e. pre-Delta, Delta and Omicron) [55]. Remdesivir also significantly reduced 28-day mortality in patients receiving high-flow oxygen/NIV at baseline, both overall (HR 0.88; 95% CI 0.82–0.93; $p < 0.0001$) and across all variant time periods ($p < 0.05$) [57]. In subgroups of immunocompromised patients [56, 58] and patients with cancer [59], remdesivir was associated with a significantly lower risk of mortality overall ($p < 0.0001$) and across all variant time periods ($p \leq 0.05$).

In an analysis of readmission data from the PINC AI Healthcare Database, 248,785 patients receiving remdesivir were matched to 191,816 patients not receiving remdesivir [60]. Remdesivir significantly ($p < 0.0001$) reduced the likelihood of 30-day readmission overall (OR 0.73; 95% CI 0.72–0.75) and across all variant time periods. Remdesivir was associated with significantly lower odds of 30-day readmission for all oxygen levels except for patients on IMV/ECMO [60].

A cohort study using health insurance claims data from the HealthVerity system was conducted in 24,856 remdesivir-exposed patients and 24,856 propensity score-matched controls [61]. The 28-day mortality rate was 0.5 per person-month in the remdesivir group and 0.6 per person-month in the control group. Remdesivir was associated with a statistically significant 17% lower risk of inpatient mortality (HR 0.83; 95% CI 0.79–0.87) [61]. In subgroups of immunocompromised patients [62] and patients admitted to the ICU [63], remdesivir significantly reduced the likelihood of readmission at 30, 60 and 90 days, irrespective of the predominant circulating variant (Delta or Omicron).

In another study, data were obtained from a multihospital health system for 42,473 patients who received at least one dose of remdesivir for COVID-19 [64]. Of these, 18,328 patients were matched to controls using time-dependent propensity scores. Patients receiving remdesivir were significantly more likely to achieve clinical improvement by day 28 (adjusted HR 1.19; 95% CI 1.16–1.22). The clinical benefit of remdesivir was greatest in patients receiving low-flow oxygen or no oxygen at baseline. Remdesivir also significantly reduced mortality in patients receiving low-flow oxygen (adjusted HR 0.85; 95% CI 0.77–0.92) [64].

5 Tolerability of Remdesivir

Remdesivir was generally well tolerated in clinical trials in hospitalized patients with COVID-19 [26, 30, 35]. In the pivotal ACTT-1 trial, the most common (incidence ≥ 5%) non-serious adverse events (AEs) reported in patients receiving remdesivir were decreased eGFR (10 vs 14% with placebo), decreased haemoglobin (9 vs 12%), decreased lymphocyte count (8 vs 11%), anaemia (8 vs 10%), increased blood glucose (7 vs 5%), pyrexia (7 vs 6%), hyperglycaemia (6 vs 7%) and increased blood creatinine (6 vs 7%) [26]. Serious AEs occurred in 24% of remdesivir recipients and 32% of placebo recipients ($p = 0.01$), including serious respiratory failure (9 vs 16%). Rates of treatment-related AEs (8 vs 9%), grade 3 or 4 AEs (51 vs 57%) and discontinuation due to AEs (11 vs 15%) were similar across both treatment groups. No deaths were considered to be related to study treatment [26].

In the SIMPLE-severe [30] and SIMPLE-moderate [35] trials, the overall incidence of AEs was similar between hospitalized patients receiving a 5-day course of remdesivir (70% in SIMPLE-severe and 51% in SIMPLE-moderate) and those receiving a 10-day course of remdesivir (74% and 59%, respectively); the incidence of AEs in patients receiving SOC alone in SIMPLE-moderate was 45% [35]. The most common AE in both trials was nausea, occurring in 10% of 5-day remdesivir recipients and 9% of 10-day remdesivir recipients in each study (vs 3% of patients receiving SOC alone in SIMPLE-moderate) [30, 35]. The incidence of grade ≥ 3 AEs was 30% and 43% in the 5-day and 10-day remdesivir groups, respectively, in SIMPLE-severe [30] and 10% and 12% of patients in the respective groups in SIMPLE-moderate (vs 12% with SOC alone) [35]. Serious AEs occurred in 21% and 35% of patients in the 5-day and 10-day remdesivir groups, respectively, in SIMPLE-severe [30] and in 5% of patients in each remdesivir group in SIMPLE-moderate (vs 9% of patients receiving SOC alone) [35] AEs leading to discontinuation of study medication occurred in 4% and 10% of patients in the 5-day and 10-day remdesivir groups, respectively, in SIMPLE-severe [30] and in 2% and 4% of patients in the respective groups in SIMPLE-moderate [35].

Overall, remdesivir was generally well tolerated when administered in combination with baricitinib [43], interferon-β-1a [44] or tocilizumab [45] in hospitalized patients with COVID-19. In ACTT-2, the combination of remdesivir plus baricitinib was associated with significantly fewer serious AEs than remdesivir plus placebo (16 vs 21%; $p = 0.03$) [43]. However, in ACTT-3, the combination of remdesivir plus interferon-β-1a was associated with more

AEs than remdesivir plus placebo, both in patients who did (69 vs 39%) and did not (7 vs 3%) require high-flow oxygen at baseline [44]. In REMDACTA, the incidence of AEs was 75% with remdesivir plus tocilizumab and 69% with remdesivir plus placebo [45].

Remdesivir had an acceptable safety profile in outpatients with COVID-19 at high risk for disease progression [47]. In PINETREE, the overall incidence of AEs was 42% with remdesivir and 46% with placebo. The most common (incidence ≥ 5%) non-serious AEs reported in patients receiving remdesivir were nausea (11 vs 7% with placebo) and headache (6 vs 6%). The incidence of treatment-related AEs was 12% with remdesivir and 9% with placebo. Serious AEs occurred in 2% of patients in the remdesivir group and 7% of patients in the placebo group. Few AEs led to discontinuation of study medication (1 vs 2%) [47]. An analysis of renal, hepatic and cardiac safety demonstrated that remdesivir was not associated with organ-specific toxicities [107]. The median change from baseline in renal (creatinine clearance) and hepatic [alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin] laboratory parameters was similar between treatment groups. There were no AEs related to nephrotoxicity. The incidence of hepatic AEs (i.e. increased ALT and AST; Sect. 5.1) and cardiac-related AEs was also similar between the remdesivir and placebo groups [107].

5.1 Adverse Events of Special Interest

There have been reports of elevated transaminases in patients receiving remdesivir in clinical trials [6, 7]. Increased ALT or AST levels occurred in 2–3% of remdesivir recipients in ACTT-1 (vs 5–6% with placebo) [26]. Grade 3 or 4 increases in ALT or AST occurred in 6–8% of remdesivir recipients in SIMPLE-severe [30] and 1–3% of remdesivir recipients in SIMPLE-moderate (vs 6–8% with SOC alone) [35]. ALT was increased in 8% of (paediatric) patients in CARAVAN [49]. Few (out)patients (< 1%) in PINETREE experienced ALT or AST elevation [107]. Liver function should be assessed prior to initiation of remdesivir and monitored during treatment as clinically appropriate [6, 7], with consideration of the risk-benefit ratio in patients with hepatic impairment (Sect. 5.3).

Hypersensitivity reactions, including infusion-related reactions and anaphylactic reactions, can occur with remdesivir [6, 7]. Signs and symptoms of hypersensitivity may be prevented with a slower infusion rate (maximum infusion time ≥ 120 min). If signs and symptoms of a clinically significant hypersensitivity reaction occur, remdesivir should be discontinued immediately and appropriate treatment should be initiated [6, 7].

5.2 Adverse Drug Reactions in the Real-World Setting

Real-world data on adverse drug reactions (ADRs) with remdesivir in patients with COVID-19 were obtained from VigiBase, the WHO Global Database of Individual Case Safety Reports (ICSRs) [108], and Eudravigilance, the centralized European database of ADR reports [109]. Among 4944 ICSRs with remdesivir in VigiBase, 21% were indicative of severe/critical disease and 22% were fatal [108]. Among 1375 ICSRs with remdesivir in Eudravigilance, 82% were serious and almost one-third were fatal [109]. In both databases, the most commonly reported ADRs associated with remdesivir involved the kidneys, liver, and heart [108, 109]. A retrospective Japanese study demonstrated that the safety of remdesivir was comparable between older (≥ 80 years of age) and younger (< 80 years of age) patients [110].

Remdesivir was associated with an increased risk of AKI [111] and acute renal failure [112] in patients with COVID-19, according to pharmacovigilance analyses of VigiBase [111] and the US FDA Adverse Event Reporting System (FAERS or AERS) database [112]. There were 589 cases of AKI [reporting OR (ROR) 2.81; 95% CI 2.48–3.18] [112] and 138 cases of acute renal failure (ROR 20.3; 95% CI 15.7–26.3; $p < 0.0001$ vs comparative drugs) [111] with remdesivir. The mean time to onset of AKI was 4.91 days [112] and most (94%) cases of acute renal failure were serious [111]. Conversely, an updated analysis of data from FAERS suggested that remdesivir may not be nephrotoxic [113]. In this analysis, signals of both remdesivir-associated AKI and renal disorders in patients with COVID-19 diminished during Q3 of 2022, with RORs of 1.50 (95% CI 0.91–2.45) and 1.69 (95% CI 1.06–2.70), respectively [113]. Moreover, a retrospective propensity score-matched analysis demonstrated that remdesivir may have a nephroprotective effect in patients with COVID-19 [114]. In this observational cohort study ($n = 927$), remdesivir was associated with a significantly lower likelihood of AKI relative to the non-remdesivir group (OR 0.40; 95% CI 0.24–0.67; $p < 0.001$) [114].

Use of remdesivir was associated with an increased risk of hepatic impairment [115] and hepatobiliary ADRs [116] in patients with COVID-19, according to pharmacovigilance analyses of VigiBase. There were 130 hepatic disorders (ROR 1.94; 95% CI 1.54–2.45) [115] and 752 hepatobiliary ADRs [116] with remdesivir, most of which were serious [115, 116]. The mean time to onset of hepatic disorders was 5.4 days [115]. Specific ADRs included increased liver transaminases (Sect. 5.1), increased bilirubin, liver failure, and hepatitis [115, 116]. However, in a retrospective propensity-score matched analysis, there was no association between remdesivir and acute liver injury (OR 0.47; 95% CI 0.20–1.11) [114].

Remdesivir was associated with an increased risk of cardiovascular ADRs in patients with COVID-19 [117, 118]. According to VigiBase, after adjusting for multiple confounders, cardiac arrest (adjusted OR 1.88; 95% CI 1.08–3.29), bradycardia (adjusted OR 2.09; 95% CI 1.24–3.53) and hypotension (adjusted OR 1.67; 95% CI 1.03–2.73) were significantly associated with the use of remdesivir [118]. Pooled data from real-world observational studies also demonstrated that remdesivir was associated with an increased risk of bradyarrhythmia (OR 3.27; 95% CI 1.90–5.63) [117]. However, in a retrospective analysis, remdesivir-induced bradycardia was transient and was not associated with ICU admission or mortality [119].

Use of remdesivir was not associated with an increased risk of neuropsychological ADRs in patients with COVID-19 [120]. Although VigiBase identified 108 neuropsychological ADRs (64 neurological events and 44 psychological events) with remdesivir, no statistically significant pharmacovigilance signal was detected [120].

5.3 Safety in Special Populations

Remdesivir was safe and well tolerated in patients with moderate COVID-19 and hepatic impairment [121]. In an exploratory analysis of the SIMPLE-moderate trial (Sect. 4.1.4), the safety profile of remdesivir (in terms of the incidence of serious AEs, ≥ grade 3 AEs, hepatobiliary AEs, and liver function investigations) was similar in patients with normal and elevated [i.e. 1–5 x upper limit of normal (ULN)] ALT levels at baseline [121]. However, due to a lack of data, remdesivir should only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk [7]. Remdesivir should not be initiated in patients with ALT ≥ 5 x ULN at baseline [6, 7]. Remdesivir should be discontinued in patients who develop ALT elevation with signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalized ratio during treatment. Remdesivir should also be discontinued in patients who develop ALT ≥ 5 x ULN during treatment, but may be restarted when ALT is < 5 x ULN [6, 7].

Remdesivir was safe and well tolerated in COVID-19 patients with renal impairment [50, 92, 93, 122–125]. In the REDPINE trial (Sect. 4.5), remdesivir had a similar AE profile to that of placebo in patients with moderately and severely reduced kidney function, and no new safety signals were identified [50]. Regardless of baseline kidney disease status (i.e. CKD or AKI), similar proportions of patients treated with remdesivir and placebo developed worsening AKI, required renal replacement therapy, or died by day 29 [50]. In real-world studies, remdesivir was not associated with a significantly increased risk of AKI in COVID-19 patients with renal failure [124] and various levels of renal impairment (i.e. estimated creatinine clearance < 30 mL/min [122], eGFR < 30 mL/min/1.73 m^2 [92] and eGFR ≥ 50 mL/min/1.73 m^2 [125]). Remdesivir was also safe and well tolerated in dialysis-dependent patients with ESRD and moderate to severe COVID-19 [123], and appeared safe in kidney transplant recipients with COVID-19 [93, 126]. As clinically appropriate, eGFR should be measured prior to and during remdesivir treatment [7]. Due to limited safety data, patients with severe renal impairment and ESRD should be closely monitored for adverse events during treatment with remdesivir [7].

Remdesivir was safe and well tolerated in paediatric patients (aged 28 days to < 18 years) with COVID-19 [49, 52, 78]. In the CARAVAN trial (Sect. 4.4), which included safety and tolerability as primary endpoints, 21% of patients experienced serious AEs, none of which were related to treatment. Grade ≥ 3 treatment-related AEs occurred in 6% of patients. The most common (incidence ≥ 5%) AEs were constipation (17%), AKI (11%), hyperglycaemia (9%), pyrexia (9%), increased ALT (8%), hypertension (8%), hypomagnesaemia (8%), vomiting (8%), anaemia (6%), nausea (6%), agitation (6%) and bradycardia (6%). No new safety trends for remdesivir were observed [49]. Among paediatric patients who received compassionate use remdesivir (Sect. 4.6), the incidence of serious AEs was 16% [52]. The only serious AE that occurred in more than one patient was elevated transaminases, and most AEs were related to COVID-19 or comorbid conditions [52]. No remdesivir-related AEs were reported in a retrospective cohort study of immunocompromised paediatric oncology patients with mild COVID-19 [78].

Remdesivir was safe and well tolerated in pregnant women with COVID-19 [22, 51]. In the IMPAACT 2032 study (Sect. 3.1), eight of ten pregnant women experienced grade 3 or 4 AEs, none of which were related to remdesivir treatment [22]. Compassionate use remdesivir (Sect. 4.6) was generally well tolerated in pregnant or postpartum women with severe COVID-19, and no new safety signals were identified [51]. However, due to limited data [6, 7], remdesivir should be avoided during pregnancy unless clinically necessary [7]. It is unknown if remdesivir is present in human breast milk [6, 7]. Therefore, breastfeeding patients should choose between discontinuing breastfeeding and discontinuing/abstaining from treatment with remdesivir [7], taking into consideration the benefits of breastfeeding for the infant and the clinical benefits of remdesivir therapy for the mother [6, 7].

6 Dosage and Administration of Remdesivir

In the USA, remdesivir is indicated for the treatment of COVID-19 in adults and paediatric patients (aged ≥ 28 days and weighing ≥ 3 kg) with positive results of

direct SARS-CoV-2 viral testing who are hospitalized, or not hospitalized, have mild-to-moderate COVID-19 and are at high risk for progression to severe COVID-19, including hospitalization or death [6]. In the EU, remdesivir is indicated for the treatment of COVID-19 in adults and paediatric patients (aged ≥ 4 weeks and weighing ≥ 3 kg) with pneumonia requiring supplemental oxygen, and in adults and paediatric patients (weighing ≥ 40 kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 (including outpatients) [7]. The efficacy and safety of remdesivir in paediatric patients aged < 4 weeks or weighing < 3 kg have not been established [6, 7].

Remdesivir is available as a solution and/or lyophilized powder for intravenous infusion over 30–120 min [6, 7]. The recommended dosage regimen for adults and paediatric patients weighing ≥ 40 kg is a single loading dose of 200 mg on day 1 followed by once-daily maintenance doses of 100 mg from day 2 onwards. The recommended dosage regimen for paediatric patients weighing 3 kg to < 40 kg is a single loading dose of 5 mg/kg on day 1 followed by 2.5 mg/kg once daily from day 2 onwards [6, 7]. In hospitalized patients (USA) [6] and in patients with pneumonia requiring supplemental oxygen (EU) [7], the recommended duration of treatment is ≥ 5 days and ≤ 10 days. In non-hospitalized patients who are at high risk for progression to severe COVID-19 (USA) [6] and in patients who do not require supplemental oxygen and are at increased risk for progressing to severe COVID-19 (EU) [7], the recommended total duration of treatment is 3 days, starting as soon as possible after diagnosis and within 7 days of symptom onset [6, 7].

Consult local prescribing information for further detailed information regarding contraindications, drug interactions, warnings and precautions, and use in special patient populations.

7 Place of Remdesivir in the Management of COVID-19

Due to its antiviral activity against coronaviruses, remdesivir has received a great deal of attention during the current COVID-19 global pandemic. Given the rapidly evolving nature of the pandemic, living guidelines for the treatment of COVID-19 are regularly updated based on new evidence [127]. The most recently updated living guidelines from the WHO [128, 129], the UK National Institute for Health and Care Excellence [130], the US National Institutes of Health (NIH) [131], the Infectious Diseases Society of America [132], the American College of Physicians [133, 134], the European Society of Clinical Microbiology and Infectious Diseases [135] and the European Respiratory Society [136] all include remdesivir in their treatment recommendations. Generally, most guidelines conditionally recommend the use of remdesivir for patients with severe COVID-19, including those requiring supplemental oxygen or NIV, and for patients with mild to moderate (non-severe) COVID-19 who are at high risk of progression to severe COVID-19 [128–135]. In addition, most guidelines specifically recommend against the use of remdesivir for patients with critical COVID-19 (e.g. those requiring IMV and/or ECMO) [128–130, 132–134, 136].

Based on data from the ACTT-1 (Sect. 4.1.1) and SIMPLE-severe (Sect. 4.1.2) trials, remdesivir received an emergency use authorization for the treatment of COVID-19 in the USA, followed by conditional approval in several other regions, including the EU. Remdesivir is fully approved for the treatment of hospitalized patients with COVID-19 (including those on supplemental oxygen), and for the treatment of outpatients with COVID-19 who are at high risk for progression to severe disease (Sect. 6). [17]. The drug is available in two formulations: a solution and a lyophilized powder (Sect. 6), which have comparable pharmacokinetics (Sect. 3).

Evidence for the benefit of remdesivir in hospitalized patients with COVID-19 was first demonstrated in the pivotal, double-blind ACTT-1 trial, in which remdesivir significantly reduced time to recovery relative to placebo (Sect. 4.1.1). This study also indicated a greater effect of remdesivir in patients receiving low-flow oxygen at baseline, albeit this may be partly explained by the larger sample size in this category [26]. Subsequent clinical trials provided additional support for the efficacy of remdesivir in terms of recovery in hospitalized patients with moderate (Sect. 4.1.4) and severe (Sect. 4.1.2) COVID-19. The SIMPLE trials also found that a 5-day course of remdesivir was effective in patients who did not require mechanical ventilation or ECMO (Sects. 4.1.2 and 4.1.4). The differences between the 5- and 10-day courses of remdesivir may been due to imbalances in baseline characteristics [30], patient care and discharge practices [35] between treatment groups, and/or the potential negative impact of additional days of hospitalization in the 10-day group [35]. The interpretation of these results is also limited by the open-label study designs of both SIMPLE trials [30, 35] and the lack of a randomized placebo group in SIMPLE-severe [30]. It should also be noted that due to the urgent circumstances under which the trials were conducted, the effects of remdesivir on SARS-CoV-2 viral load were not evaluated [30, 35].

COVID-19 is associated with excess mortality and has become a leading cause of death worldwide [137]. Therefore, reducing mortality and preventing disease progression in hospitalized patients with moderate to severe COVID-19

is a key goal of treatment. Both ACTT-1 (Sect. 4.1.1) and SIMPLE-severe (Sect. 4.1.2) showed a mortality benefit for remdesivir over placebo or SOC, although this was assessed as a secondary endpoint. Preliminary data from the large WHO SOLIDARITY trial suggested that remdesivir had little or no effect on mortality in hospitalized patients with COVID-19 (Sect. 4.1.5). However, updated results of WHO SOLIDARITY demonstrated that although remdesivir had no significant effect on mortality in patients who were already being ventilated, it had a small but statistically significant effect against death or progression to ventilation among other hospitalized patients (Sect. 4.1.5). This provides support for previous findings that remdesivir may be more effective in hospitalized patients with minimal oxygen requirements at baseline (Sect. 4.1.1).

Systematic reviews and meta-analyses of randomized controlled trials investigating the use of remdesivir in hospitalized patients with COVID-19 have yielded equivocal results [138–143]. Some analyses demonstrated a possible reduction in mortality with remdesivir, particularly in patients requiring low or no oxygen support [138, 141, 143], while other analyses showed that remdesivir had little to no effect on mortality [139, 140, 142]. It should be noted that most of the randomized controlled trials included in these analyses were not powered to assess mortality. Most analyses demonstrated that remdesivir was associated with improved recovery in hospitalized patients with COVID-19 [138–140, 142, 143].

Data from real-world studies (Sect. 4.7) and the compassionate use program (Sect. 4.6) were generally consistent with those seen in clinical trials. In several large real-world studies, remdesivir was associated with clinical improvement, reduced mortality and/or reduced likelihood of readmission in hospitalized adults with COVID-19 (Sect. 4.7). The mortality benefit of remdesivir in these studies was seen irrespective of baseline oxygen requirements and across different variants of concern (Sect. 4.7). These studies also demonstrated that remdesivir reduced the likelihood of readmission and mortality in subgroups of immunocompromised patients (Sect. 4.7). This is a notable finding, given that immunocompromised patients are at increased risk of hospitalization, complications and mortality from COVID-19 [56]. Despite their inherent limitations, such observational studies may offer a better representation of real-life clinical practice than prospective clinical trials, further supporting the effectiveness of remdesivir for the treatment of COVID-19.

Early outpatient treatment of COVID-19 is important for patients who are at increased risk for progression to severe disease [144]. In the PINETREE trial, remdesivir reduced the risk of hospitalization or death in outpatients at high risk of progressing to severe COVID-19 (Sect. 4.3). This led to an expanded indication for remdesivir, which was initially approved only for the treatment of hospitalized patients with COVID-19. In subgroup analyses of PINETREE, remdesivir appeared to be more effective when initiated early in the course of disease (Sect. 4.3). This finding is consistent with post hoc analyses of the ACTT-1 trial, which demonstrated that remdesivir reduced the risk of progression to IMV or death in hospitalized patients with COVID-19 (Sect. 4.1.1) [47].

Although COVID-19 is generally milder in paediatric patients than in adults, some children with COVID-19, particularly those with comorbidities, may require hospitalization and specific treatment [131]. The US NIH recommends remdesivir as a treatment option for hospitalized paediatric patients with COVID-19 who require no supplemental oxygen, conventional oxygen, high-flow oxygen or NIV (but not those requiring mechanical ventilation or ECMO) [131]. The CARAVAN trial, while primarily designed to evaluate safety, tolerability, and pharmacokinetics, also demonstrated a high rate of clinical improvement with remdesivir in paediatric patients with COVID-19 (Sect. 4.4). Results from this trial supported the expanded approval of remdesivir to include paediatric patients aged ≥ 28 days (USA) or ≥ 4 weeks (EU) and weighing ≥ 3 kg (Sect. 6).

Based on the results of the REDPINE trial (Sects. 3.1 and 4.5), the EU and US labels for remdesivir were extended to treat COVID-19 in patients with severe renal impairment, including those on dialysis (Sect. 3.1). As such, remdesivir is the first antiviral for COVID-19 that can be used across all stages of renal disease. Previously, the use of remdesivir had been restricted in patients with severe renal impairment due to insufficient data [145].

Remdesivir, alone or in combination with other agents, was generally well tolerated in clinical trials in hospitalized patients with COVID-19 (Sect. 5). Remdesivir also had an acceptable safety profile in outpatients with COVID-19 at high risk of disease progression (Sect. 5). Rates of AEs of special interest such as elevated transaminases were generally low (Sect. 5.1). Nevertheless, close monitoring of liver function is recommended (Sects. 5.1 and 5.3). Real-world pharmacovigilance data have shown that the use of remdesivir was associated with an increased risk of some ADRs, including AKI, acute renal failure, hepatic impairment, hepatobiliary ADRs, and cardiovascular ADRs (Sect. 5.2). Remdesivir was safe and well tolerated in special patient populations, including paediatric patients, pregnant women, patients with hepatic impairment, and patients with renal impairment (Sect. 5.3). This is important, given that pregnant women with COVID-19 have an increased risk of severe disease and adverse pregnancy outcomes [22], and patients with underlying CKD, patients on dialysis, and kidney transplant recipients are at higher risk for severe COVID-19 and mortality [146, 147].

To date, few well-designed, randomized controlled trials have directly compared remdesivir with other pharmacological agents in patients with COVID-19. In the WHO SOLIDARITY trial, which investigated four treatment options (remdesivir, lopinavir/ritonavir, interferon-β-1a and hydroxychloroquine), each drug was compared with its own control (Sect. 4.1.5). None of the treatments significantly reduced the overall risk of mortality in WHO SOLIDARITY (Sect. 4.1.5) or in meta-analyses of WHO SOLIDARITY and other randomized controlled trials [36, 37]. However, monoclonal antibodies are no longer recommended for the treatment of COVID-19. A systematic review demonstrated some apparent differences in efficacy between remdesivir and various other antivirals (including nirmatrelvir plus ritonavir and molnupiravir), but no significant differences in tolerability [148]. However, given the limitations of indirect comparisons, these results should be interpreted with caution. Unlike nirmatrelvir plus ritonavir, which is administered orally [149, 150] and may be more convenient for outpatients, remdesivir is administered as an intravenous infusion over 30–120 min (Sect. 6). However, nirmatrelvir plus ritonavir has the potential for numerous drug-drug interactions [149, 150], while the possibility of drug-drug interactions with remdesivir appears to be low (Sect. 3.2). Clinical trials directly comparing remdesivir with other antivirals such as nirmatrelvir plus ritonavir would help to definitively place remdesivir in the management of COVID-19.

The COVID-19 pandemic has placed a significant economic burden on healthcare systems, with total global mortality costs estimated to be in the trillions [151]. Therefore, cost-effective treatments that reduce the mortality of COVID-19 are vital. A cost-effectiveness analysis conducted alongside the CATCO trial (Sect. 4.1.5.2) found that, from a Canadian healthcare payer perspective, remdesivir plus usual care was cost effective relative to usual care alone in hospitalized patients with COVID-19 [152]. Other studies also found that remdesivir was cost effective relative to SOC in hospitalized patients with COVID-19 in China, South Africa, Turkey and the United Arab Emirates [153, 154], while studies conducted in the USA showed conflicting results [153, 155].

In two studies, remdesivir was estimated to be cost effective only if it prevented death in hospitalized patients with COVID-19 [156, 157]. A Markov model analyzing the cost-effectiveness of remdesivir from the perspective of the US healthcare sector estimated the incremental cost-effectiveness ratio (ICER) of remdesivir to be $US298,200 per quality-adjusted life-year (QALY) without mortality benefit and $US50,100 per QALY with mortality benefit [156]. In a probabilistic cost-effectiveness analysis of remdesivir in England and Wales, corresponding ICERs were > £1 million per QALY without mortality benefit and £12,400 per QALY with mortality benefit [157]. Remdesivir had a 74% probability of being cost effective at a willingness-to-pay threshold of £20,000 per QALY [157]. Further robust pharmacoeconomic data would be beneficial.

In conclusion, remdesivir is effective and generally well tolerated in patients with COVID-19, including hospitalized patients with moderate or severe COVID-19 and minimal oxygen requirements, and outpatients who are at high risk for disease progression. However, remdesivir appears to be less effective in hospitalized patients with severe disease who are already being mechanically ventilated. Overall, remdesivir represents a useful treatment option for patients with COVID-19, particularly those who require supplemental oxygen.

Data Selection Remdesivir: 1669 records identified

Duplicates removed	26
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	996
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	490
Cited efficacy/tolerability articles	105
Cited articles not efficacy/tolerability	52

Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were remdesivir, Veklury, GS-5734, coronavirus, SARS-CoV-2, COVID-19, 2019-nCoV. Records were limited to those in English language. Searches last updated 17 Jul 2023

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40265-023-01926-0.

Acknowledgements During the peer review process, the manufacturer of remdesivir was also offered an opportunity to review this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

Declarations

Funding The preparation of this review was not supported by any external funding.

Authorship and Conflict of Interest Hannah A. Blair is a salaried employee of Adis International Ltd/Springer Nature and declares no relevant conflicts of interest. All authors contributed to the review and are responsible for the article content.

Ethics Approval, Consent to Participate, Consent to Publish, Availability of Data and Material, Code Availability Not applicable.

References

1. Blann AD, Heitmar R. SARS-CoV-2 and COVID-19: a narrative review. Br J Biomed Sci. 2022;79:10426.
2. Cascella M, Rajnik M, Aleem A, et al. Features, evaluation, and treatment of coronavirus (COVID-19) [updated 13 Oct 2022]. In: StatPearls [Internet]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554776/.
3. Ansems K, Grundeis F, Dahms K, et al. Remdesivir for the treatment of COVID-19. Cochrane Database Syst Rev. 2021;8(8):Cd014962.
4. Alotaibi F. Current strategies in diagnostics and therapeutics against novel coronavirus disease (COVID-19). Acta Pharm. 2022;72(2):171–97.
5. Malin JJ, Suárez I, Priesner V, et al. Remdesivir against COVID-19 and other viral diseases. Clin Microbiol Rev. 2020;34(1):e00162-e220.
6. Gilead Sciences I. VEKLURY-remdesivir injection, powder, lyophilized, for solution: US prescribing information. 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214787s019lbl.pdf. Accessed 21 Jul 2023.
7. Gilead Sciences. Veklury 100 mg powder for concentrate for solution for infusion: EU summary of product characteristics. 2023. https://www.ema.europa.eu/en/medicines/human/EPAR/veklury. Accessed 21 Jul 2023.
8. Gordon CJ, Tchesnokov EP, Woolner E, et al. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. J Biol Chem. 2020;295(20):6785–97.
9. Tchesnokov EP, Gordon CJ, Woolner E, et al. Template-dependent inhibition of coronavirus RNA-dependent RNA polymerase by remdesivir reveals a second mechanism of action. J Biol Chem. 2020;295(47):16156–65.
10. Rodriguez L, Hsiang T-Y, Li J, et al. Remdesivir retains potent activity against SARS-CoV-2 variants of concern [poster]. In: 30th Conference on Retroviruses and Opportunistic Infections. 2023.
11. Pruijssers AJ, George AS, Schäfer A, et al. Remdesivir inhibits SARS-CoV-2 in human lung cells and chimeric SARS-CoV expressing the SARS-CoV-2 RNA polymerase in mice. Cell Rep. 2020;32(3):107940.
12. Williamson BN, Feldmann F, Schwarz B, et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. Nature. 2020;585(7824):273–6.
13. Checkmahomed L, Carbonneau J, Du Pont V, et al. In vitro selection of remdesivir-resistant SARS-CoV-2 demonstrates high barrier to resistance. Antimicrob Agents Chemother. 2022;66(7):e0019822.
14. Rodriguez L, Lee HW, Li J, et al. Remdesivir resistance analyses from the PINETREE study in outpatients with COVID-19 [poster]. In: 30th Conference on Retroviruses and Opportunistic Infections. 2023.
15. Santos Bravo M, Alonso R, Soria D, et al. Genetic study of SARS-CoV-2 non structural protein 12 in COVID-19 patients non responders to remdesivir. Microbiol Spectr. 2022;10(6):e0244822.
16. Focosi D, Maggi F, McConnell S, et al. Very low levels of remdesivir resistance in SARS-COV-2 genomes after 18 months of massive usage during the COVID19 pandemic: a GISAID exploratory analysis. Antiviral Res. 2022;198: 105247.
17. Humeniuk R, Mathias A, Cao H, et al. Safety, tolerability, and pharmacokinetics of remdesivir, an antiviral for treatment of COVID-19, in healthy subjects. Clin Transl Sci. 2020;13(5):896–906.
18. Leegwater E, Moes D, Bosma LBE, et al. Population pharmacokinetics of remdesivir and GS-441524 in hospitalized COVID-19 patients. Antimicrob Agents Chemother. 2022;66(6):e0025422.
19. Tamura R, Irie K, Nakagawa A, et al. Population pharmacokinetics and exposure-clinical outcome relationship of remdesivir major metabolite GS-441524 in patients with moderate and severe COVID-19. CPT Pharmacometrics Syst Pharmacol. 2023;12(4):513–21.
20. Ahmed A, Rojo P, Agwu A, et al. Remdesivir treatment for COVID-19 in hospitalized children: CARAVAN interim results [abstract no. 05114 plus oral presentation]. In: 32nd European Society of Clinical Microbiology and Infectious Diseases. 2022.
21. Tempestilli M, Ascoli Bartoli T, Benvenuto D, et al. Interpatient variability in the pharmacokinetics of remdesivir and its main metabolite GS-441524 in treated COVID-19 subjects. J Antimicrob Chemother. 2022;77(10):2683–7.
22. Brooks KM, Baltrusaitis K, Momper J, et al. IMPAACT 2032: remdesivir PK safety in pregnant and non-pregnant women with COVID-19 [abstract no. 676]. Top Antivir Med. 2022;30(1 Suppl):267.
23. Humeniuk R, Deng R, Sorribes IC, et al. Pharmacokinetics inform remdesivir dosing for patients with severe renal impairment [poster 514]. In: 30th Conference on Retroviruses and Opportunistic Infections. 2023.
24. Humeniuk R, Mathias A, Kirby BJ, et al. Pharmacokinetic, pharmacodynamic, and drug-interaction profile of remdesivir, a SARS-CoV-2 replication inhibitor. Clin Pharmacokinet. 2021;60(5):569–83.
25. Nies AT, König J, Hofmann U, et al. Interaction of remdesivir with clinically relevant hepatic drug uptake transporters. Pharmaceutics. 2021;13(3):1–8.
26. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - final report. N Engl J Med. 2020;383(19):1813–26.
27. Paules CI, Gallagher SK, Rapaka RR, et al. Remdesivir for the prevention of invasive mechanical ventilation or death in coronavirus disease 2019 (COVID-19): a post hoc analysis of the Adaptive COVID-19 Treatment Trial-1 cohort data. Clin Infect Dis. 2022;74(7):1260–4.
28. Fintzi J, Bonnett T, Sweeney DA, et al. Deconstructing the treatment effect of remdesivir in the Adaptive Coronavirus Disease 2019 (COVID-19) Treatment Trial-1: implications for critical care resource utilization. Clin Infect Dis. 2022;74(12):2209–17.
29. Thiede JM, Gress AR, Libby SD, et al. Immune profiling to determine early disease trajectories associated with coronavirus disease 2019 mortality rate: a substudy from the ACTT-1 trial. J Infect Dis. 2021;223(8):1339–44.

30. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe covid-19. N Engl J Med. 2020;383(19):1827–37.
31. Olender SA, Perez KK, Go AS, et al. Remdesivir for severe coronavirus disease 2019 (COVID-19) versus a cohort receiving standard of care. Clin Infect Dis. 2021;73(11):e4166–74.
32. Olender SA, Walunas TL, Martinez E, et al. Remdesivir versus standard-of-care for severe coronavirus disease 2019 infection: an analysis of 28-day mortality. Open Forum Infect Dis. 2021;8(7):ofab278.
33. Go AS, Malenica I, Fusco D, et al. Remdesivir vs. standard of care for severe Covid-19 [abstract no. 2969 plus poster]. In: World Microbe Forum. 2021.
34. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395(10236):1569–78.
35. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA. 2020;324(11):1048–57.
36. WHO Solidarity Trial Consortium, et al. Repurposed antiviral drugs for Covid-19—interim WHO Solidarity trial results. N Engl J Med. 2021;384(6):497–511.
37. WHO Solidarity Trial Consortium, et al. Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses. Lancet. 2022;399(10339):1941–53.
38. Ader F, Bouscambert-Duchamp M, Hites M, et al. Remdesivir for the treatment of hospitalised patients with COVID-19: final results from the DisCoVeRy randomised, controlled, open-label trial. medRxiv. 2022. https://doi.org/10.1101/2022.03.30.22273206.
39. Ader F, Bouscambert-Duchamp M, Hites M, et al. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial. Lancet Infect Dis. 2022;22(2):209–21.
40. Lingas G, Néant N, Gaymard A, et al. Effect of remdesivir on viral dynamics in COVID-19 hospitalized patients: a modelling analysis of the randomized, controlled, open-label DisCoVeRy trial. J Antimicrob Chemother. 2022;77(5):1404–12.
41. Ali K, Azher T, Baqi M, et al. Remdesivir for the treatment of patients in hospital with COVID-19 in Canada: a randomized controlled trial. CMAJ. 2022;194(7):e242–51.
42. Barratt-Due A, Olsen IC, Nezvalova-Henriksen K, et al. Evaluation of the effects of remdesivir and hydroxychloroquine on viral clearance in COVID-19: a randomized trial. Ann Intern Med. 2021;174(9):1261–9.
43. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. N Engl J Med. 2021;384(9):795–807.
44. Kalil AC, Mehta AK, Patterson TF, et al. Efficacy of interferon beta-1a plus remdesivir compared with remdesivir alone in hospitalised adults with COVID-19: a double-bind, randomised, placebo-controlled, phase 3 trial. Lancet Respir Med. 2021;9(12):1365–76.
45. Rosas IO, Diaz G, Gottlieb RL, et al. Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. Intensive Care Med. 2021;47(11):1258–70.
46. Mohiuddin Chowdhury ATM, Kamal A, Abbas KU, et al. Efficacy and outcome of remdesivir and tocilizumab combination against dexamethasone for the treatment of severe COVID-19: a randomized controlled trial. Front Pharmacol. 2022;13:690726.
47. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. N Engl J Med. 2022;386(4):305–15.
48. Brown SM, Katz MJ, Ginde AA, et al. Consistent effects of early remdesivir on symptoms and disease progression across at-risk outpatient subgroups: treatment effect heterogeneity in PINETREE study. Infect Dis Ther. 2023;12(4):1189–203.
49. Ahmed A, Rojo P, Agwu A, et al. Remdesivir treatment for Covid-19 in hospitalized children: CARAVAN interim results [abstract no. 744 plus poster]. Top Antivir Med. 2022;30(1 Suppl.):296–7.
50. Santos Fernandez JR, Goldman JD, Tuttle KR, et al. Efficacy and safety of remdesivir in people with moderately and severely reduced kidney function hospitalised for COVID-19: the RED-PINE study [abstract no. P2635 plus poster]. In: 33rd European Congress of Clinical Microbiology and Infectious Diseases. 2023.
51. Burwick RM, Yawetz S, Stephenson KE, et al. Compassionate use of remdesivir in pregnant women with severe coronavirus disease 2019. Clin Infect Dis. 2021;73(11):e3996–4004.
52. Goldman DL, Aldrich ML, Hagmann SHF, et al. Compassionate use of remdesivir in children with severe COVID-19. Pediatrics. 2021;147(5):1–9.
53. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med. 2020;382(24):2327–36.
54. Maserati R, Khosravi A, Bhagani S, et al. Exposure to remdesivir through compassionate use: safety and efficacy in 163 patients [abstract no. 11813 plus poster]. In: COVID-19 Conference (Virtual). 2020.
55. Mozaffari E, Chandak A, Gottlieb RL, et al. Remdesivir reduces mortality in hospitalized COVID-19 patients across variant eras [abstract no. 556 plus poster]. In: 30th Conference on Retroviruses and Opportunistic Infections. 2023.
56. Mozaffari E, Chandak A, Gottlieb RL, et al. Remdesivir reduces mortality in immunocompromised patients hospitalized for COVID-19 [abstract no. 557 plus poster]. In: 30th Conference on Retroviruses and Opportunistic Infections. 2023.
57. Mozaffari E, Chandak A, Gottlieb RL, et al. Remdesivir is associated with decreased mortality in hospitalised COVID-19 patients requiring high-flow oxygen in the United States [oral presentation]. In: 33rd European Congress of Clinical Microbiology and Infectious Diseases. 2023.
58. Mozaffari E, Chandak A, Kalil AC, et al. Immunocompromised patients hospitalized for COVID-19 in the United States: evolving patient characteristics and clinical outcomes across emerging variants [poster LB081]. In: 33rd European Congres of Clinical Microbiology and Infectious Diseases. 2023.
59. Mozaffari E, Chandak A, Chima-Melton C, et al. Remdesivir is associated with lower mortality in cancer patients hospitalized for COVID-19 across emerging variants [poster LB074]. In: 33rd European Congress of Clinical Microbiology and Infectious Diseases. 2023.
60. Mozaffari E, Chandak A, Gottlieb RL, et al. Remdesivir is associated with reduced readmission after COVID-19 hospitalization [abstract no. 558 plus poster]. In: 30th Conference on Retroviruses and Opportunistic Infections. 2023.
61. Chokkalingam AP, Hayden J, Goldman JD, et al. Association of remdesivir treatment with mortality among hospitalized adults with COVID-19 in the United States. JAMA Netw Open. 2022;5(12): e2244505.
62. Lee E, Gupta RS, Berry M, et al. Remdesivir reduces readmission in immunocompromised adult patients hospitalised with COVID-19 [abstract no. 06786 plus oral presentation]. In: 33rd

European Congress of Clinical Microbiology and Infectious Diseases. 2023.
63. Gupta RS, Berry M, Abdelghany M, et al. Remdesivir reduced the hazard of hospital readmission in people with COVID-19 admitted to the ICU while Delta and Omicron were the predominant circulating variants [poster LB101]. In: 33rd European Congress of Clinical Microbiology and Infectious Diseases. 2023.
64. Garibaldi BT, Wang K, Robinson ML, et al. Real-world effectiveness of remdesivir in adults hospitalized with coronavirus disease 2019 (COVID-19): a retrospective, multicenter comparative effectiveness study. Clin Infect Dis. 2022;75(1):e516–24.
65. Wong CKH, Lau KTK, Au ICH, et al. Optimal timing of remdesivir initiation in hospitalized patients with coronavirus disease 2019 (COVID-19) administered with dexamethasone. Clin Infect Dis. 2022;75(1):e499–508.
66. Slim MA, Appelman B, Peters-Sengers H, et al. Real-world evidence of the effects of novel treatments for COVID-19 on mortality: a nationwide comparative cohort study of hospitalized patients in the first, second, third, and fourth waves in the Netherlands. Open Forum Infect Dis. 2022;9(12):ofac632.
67. Ramos-Rincon JM, López-Carmona MD, Cobos-Palacios L, et al. Remdesivir in very old patients (≥80 years) hospitalized with COVID-19: real world data from the SEMI-COVID-19 registry. J Clin Med. 2022;11(13):3769.
68. Alonso R, Berenguer J, Ramírez M, et al. Early administration of remdesivir is associated with lower risk of ICU admission in hospitalised patients with COVID-19 [abstract no. P2048]. In: 32nd European Society of Clinical Microbiology and Infectious Diseases. 2022.
69. Rajme-López S, Martinez-Guerra BA, Zalapa-Soto J, et al. Early outpatient treatment with remdesivir in patients at high risk for severe COVID-19: a prospective cohort study. Open Forum Infect Dis. 2022;9(10):ofac502.
70. Marrone A, Nevola R, Sellitto A, et al. Remdesivir plus dexamethasone versus dexamethasone alone for the treatment of coronavirus disease 2019 (COVID-19) patients requiring supplemental O_2 therapy: a prospective controlled nonrandomized study. Clin Infect Dis. 2022;75(1):e403–9.
71. Petrakis V, Rapti V, Akinosoglou K, et al. Greek Remdesivir Cohort (GREC) study: effectiveness of antiviral drug remdesivir in hospitalized patients with COVID-19 pneumonia. Microorganisms. 2022;10(10):1949.
72. Spagnuolo V, Voarino M, Tonelli M, et al. Impact of remdesivir on SARS-CoV-2 clearance in a real-life setting: a matched-cohort study. Drug Des Devel Ther. 2022;16:3645–54.
73. Hasanoglu I, Guner R, Celik I, et al. Remdesivir treatment for patients with moderate to severe COVID-19. Turk J Med Sci. 2022;52(4):880–7.
74. Lakhanpal M, Sarkar D, Kumar R, et al. Reduction in the rate of mortality of moderate to severe COVID 19 infected patients with the use of remdesivir—a tertiary care hospital-based retrospective observational study. Anesth Essays Res. 2022;16(3):296–300.
75. Lucijanic M, Busic N, Bistrovic P, et al. Real-life experience with remdesivir for treatment of hospitalized coronavirus disease 2019 patients: matched case-control study from a large tertiary hospital registry. Croat Med J. 2022;63(6):536–43.
76. Marx K, Goncarova K, Fedders D, et al. Clinical outcomes of hospitalized COVID-19 patients treated with remdesivir: a retrospective analysis of a large tertiary care center in Germany. Infection. 2023;51(1):97–108.
77. Metchurtchlishvili R, Chkhartishvili N, Abutidze A, et al. Effect of remdesivir on mortality and the need for mechanical ventilation among hospitalized patients with COVID-19: real-world data from a resource-limited country. Int J Infect Dis. 2023;129:63–9.
78. Ong RYL, Seah VXF, Chong CY, et al. A cohort study of COVID-19 infection in pediatric oncology patients plus the utility and safety of remdesivir treatment. Acta Oncol. 2023;62(1):53–7.
79. Pilgram L, Appel KS, Ruethrich MM, et al. Use and effectiveness of remdesivir for the treatment of patients with covid-19 using data from the Lean European Open Survey on SARS-CoV-2 infected patients (LEOSS): a multicentre cohort study. Infection. 2023;51:1–17.
80. Yu M, Kim BI, Kim J, et al. Clinical outcomes of remdesivir-treated COVID-19 patients in South Korea. Osong Public Health Res Perspect. 2022;13(5):370–6.
81. Zamani S, Alizadeh M, Shahrestanaki E, et al. Prognostic comparison of COVID-19 outpatients and inpatients treated with remdesivir: a retrospective cohort study. PLoS ONE. 2022;17(11): e0277413.
82. Zerbit J, Detroit M, Chevret S, et al. Remdesivir for patients hospitalized with COVID-19 severe pneumonia: a national cohort study (Remdeco-19). J Clin Med. 2022;11(21):6545.
83. Gressens SB, Esnault V, De Castro N, et al. Remdesivir in combination with dexamethasone for patients hospitalized with COVID-19: a retrospective multicenter study. PLoS ONE. 2022;17(2): e0262564.
84. Padilla S, Polotskaya K, Fernández M, et al. Survival benefit of remdesivir in hospitalized COVID-19 patients with high SARS-CoV-2 viral loads and low-grade systemic inflammation. J Antimicrob Chemother. 2022;77(8):2257–64.
85. Benfield T, Bodilsen J, Brieghel C, et al. Improved survival among hospitalized patients with coronavirus disease 2019 (COVID-19) treated with remdesivir and dexamethasone. A nationwide population-based cohort study. Clin Infect Dis. 2021;73(11):2031–6.
86. Arch BN, Kovacs D, Scott JT, et al. Evaluation of the effectiveness of remdesivir in severe COVID-19 using observational data from a prospective national cohort study. medRxiv. 2022. https://doi.org/10.1101/2021.06.18.21259072.
87. Garcia-Vidal C, Alonso R, Camon AM, et al. Impact of remdesivir according to the pre-admission symptom duration in patients with COVID-19. J Antimicrob Chemother. 2021;76(12):3296–302.
88. Finn A, Jindal A, Andrea SB, et al. Association of treatment with remdesivir and 30-day hospital readmissions in patients hospitalized with COVID-19. Am J Med Sci. 2022;363(5):403–10.
89. Butt A, Talisa V, Yan P, et al. Risk of death in remdesivir treated and untreated patients with COVID-19 infection [poster]. In: 30th Conference on Retroviruses and Opportunistic Infections. 2023.
90. Mehdinezhad H, Karim B, Ahmadi N, et al. Vaccination status and outcomes of COVID-19 patients admitted to a tertiary hospital in Iran during the dominant Delta variant period. Immun Inflamm Dis. 2023;11(2): e790.
91. Eid J, Abdelwahab M, Colburn N, et al. Early administration of remdesivir and intensive care unit admission in hospitalized pregnant individuals with coronavirus disease 2019 (COVID-19). Obstet Gynecol. 2022;139(4):619–21.
92. Huynh D, Wang S, Joseph DA, et al. Remdesivir use in patients with renal impairment [abstract no. 884]. Crit Care Med. 2022;50(1 Suppl.):438.
93. Elec F, Magnusson J, Elec A, et al. COVID-19 and kidney transplantation: the impact of remdesivir on renal function and outcome—a retrospective cohort study. Int J Infect Dis. 2022;118:247–53.
94. Terkes V, Lisica K, Marusic M, et al. Remdesivir treatment in moderately ill COVID-19 patients: a retrospective single center study. J Clin Med. 2022;11(17):5066.

95. Gaspar Z, Szabo BG, Abraham A, et al. Outcomes of high-risk adult outpatients treated with early remdesivir therapy during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) omicron era: experiences from the national centre of Hungary. Naunyn Schmiedebergs Arch Pharmacol. 2023;396:1–6.
96. Mazzitelli M, Trunfio M, Sasset L, et al. Risk of hospitalization and sequelae in patients with COVID-19 treated with 3-day early remdesivir vs. controls in the vaccine and Omicron era: a real-life cohort study. J Med Virol. 2023;95(3): e28660.
97. Kintrilis N, Galinos I. Outpatient intravenous remdesivir to prevent progression to severe COVID-19: an observational study from a Greek hospital. Recent Adv Antiinfect Drug Discov. 2023. https://doi.org/10.2174/2772434418666230331083714.
98. Arribas Lopez JR, Ruiz Seco MP, Fanjul Losa F, et al. Remdesivir associated with decreased mortality in hospitalized COVID-19 patients: a real-world evidence study using natural language processing [poster P2630]. In: 33rd European Congress of Microbiology and Infectious Diseases. 2023.
99. Dobrowolska K, Zarebska-Michaluk D, Brzdek M, et al. Retrospective analysis of the effectiveness of remdesivir in COVID-19 treatment during periods dominated by Delta and Omicron SARS-CoV-2 variants in clinical settings. J Clin Med. 2023;12(6):2371.
100. Alexander H, Gunasekaran K, Sara John J, et al. Evaluation of remdesivir to the outcomes of hospitalized patients with COVID-19 infection in a tertiary-care hospital in southern India. J Infect Dev Ctries. 2023;17(3):304–10.
101. Alonso-Navarro R, Ramirez M, Masia M, et al. Time from symptoms onset to remdesivir is associated with the risk of ICU admission: a multicentric analyses. BMC Infect Dis. 2023;23(1):286.
102. Marocco R, Del Borgo C, Tortellini E, et al. Use of remdesivir in patients with SARS-CoV-2 pneumonia in a real-life setting during the second and third COVID-19 epidemic waves. Viruses. 2023;15(4):947.
103. Margalit I, Tiseo G, Ripa M, et al. Real-life experience with remdesivir for treatment of COVID-19 among older adults: a multicentre retrospective study. J Antimicrob Chemother. 2023;78(6):1505–9.
104. Rivera CG, Chesdachai S, Draper EW, et al. Clinical outcomes of COVID-19 treated with remdesivir across the continuum of care. Influenza Other Respir Viruses. 2023;17(5): e13136.
105. Attena E, Caturano A, Annunziata A, et al. Remdesivir treatment and clinical outcome in non-severe hospitalized COVID-19 patients: a propensity score matching multicenter Italian hospital experience. Eur J Clin Pharmacol. 2023;79(7):967–74.
106. Breskin A, Wiener C, Adimora AA, et al. Effectiveness of remdesivir treatment protocols among patients hospitalized with COVID-19: a target trial emulation. Epidemiology. 2023;34(3):365–75.
107. Webb B, Oguchi G, Sachdeva Y, et al. Safety of remdesivir vs placebo in nonhospitalized patients with COVID-19 [abstract no. 456 plus poster]. Top Antivir Med. 2022;30(1 Suppl.):174.
108. Rocca E, Gauffin O, Savage R, et al. Remdesivir in the COVID-19 pandemic: an analysis of spontaneous reports in VigiBase during 2020. Drug Saf. 2021;44(9):987–98.
109. Cesaro M, Rafaniello C, Di Mauro C, et al. Safety of remdesivir in COVID-19 patients: post-marketing evaluation on spontaneous adverse event reporting system [abstract no. 146 plus poster]. Eur J Clin Pharmacol. 2022;78(Suppl. 1):S116–7.
110. Kanai O, Fujita K, Nanba K, et al. Safety of remdesivir for patients 80 years of age or older with coronavirus disease 2019 (COVID-19). Drugs Aging. 2021;38(12):1067–74.
111. Gérard AO, Laurain A, Fresse A, et al. Remdesivir and acute renal failure: a potential safety signal from disproportionality analysis of the WHO safety database. Clin Pharmacol Ther. 2021;109(4):1021–4.
112. Wu B, Luo M, Wu F, et al. Acute kidney injury associated with remdesivir: a comprehensive pharmacovigilance analysis of COVID-19 reports in FAERS. Front Pharmacol. 2022;13: 692828.
113. Li X, Zhou L, Gaggl M, et al. Remdesivir for COVID-19 and acute kidney injury: disproportionality analysis of data from the U.S. Food and Drug Administration Adverse Event Reporting System. Int J Clin Pharm. 2023;45(2):509–14.
114. Lim H, Palaiodimos L, Berto CG, et al. Remdesivir in the treatment of COVID-19: a propensity score-matched analysis from a public hospital in New York City assessing renal and hepatic safety. J Clin Med. 2022;11(11):3132.
115. Montastruc F, Thuriot S, Durrieu G. Hepatic disorders with the use of remdesivir for coronavirus 2019. Clin Gastroenterol Hepatol. 2020;18(12):2835–6.
116. Kim MS, Jung SY, Lee SW, et al. Hepatobiliary adverse drug reactions associated with remdesivir: the WHO international pharmacovigilance study. Clin Gastroenterol Hepatol. 2021;19(9):1970-2.e3.
117. Al-Jammali S, Al-Zakhari R, Sheets N, et al. Bradyarrhythmia after remdesivir administration in SARS-CoV-2: a review of literature and meta-analysis of observational studies in epidemiology. Cardiol Res. 2022;13(3):135–43.
118. Jung SY, Kim MS, Li H, et al. Cardiovascular events and safety outcomes associated with remdesivir using a World Health Organization international pharmacovigilance database. Clin Transl Sci. 2022;15(2):501–13.
119. Pantazopoulos I, Mavrovounis G, Dimeas G, et al. Remdesivir-induced bradycardia is not associated with worse outcome in patients with COVID-19: a retrospective analysis. Am J Cardiovasc Drugs. 2022;22(6):705–10.
120. Lee S, Yang JW, Jung SY, et al. Neuropsychological adverse drug reactions of remdesivir: analysis using VigiBase, the WHO global database of individual case safety reports. Eur Rev Med Pharmacol Sci. 2021;25(23):7390–7.
121. Tsang O, Brar I, Spinner C, et al. Impact of baseline alanine aminotransferase levels on the safety and efficacy of remdesivir in moderate COVID-19 patients [abstract no. 120]. Hepatology (Baltimore, MD). 2020;72(1 Suppl.):88A-A89.
122. Ackley TW, McManus D, Topal JE, et al. A valid warning or clinical lore: an evaluation of safety outcomes of remdesivir in patients with impaired renal function from a multicenter matched cohort. Antimicrob Agents Chemother. 2021;65(2):1–8.
123. Aiswarya D, Arumugam V, Dineshkumar T, et al. Use of remdesivir in patients with COVID-19 on hemodialysis: a study of safety and tolerance. Kidney Int Rep. 2021;6(3):586–93.
124. Babar Z, Dodani S, Nasim A, et al. Outcome of COVID-19 in renal failure and tolerance of remdesivir: experience from a large renal and dialysis centre in Pakistan [abstract no. P2063]. In: 32nd European Society of Clinical Microbiology and Infectious Diseases. 2022.
125. Ogbuagu O, Tashima KT, Gunthard HF, et al. Acute kidney injury in patients with moderate COVID-19 treated with RDV versus SOC [abstract no. 395]. Top Antivir Med. 2021;29(1):140.
126. Latief M, Abbas F, Iqbal M, et al. Remdesivir in renal transplant patients with coronavirus disease 2019: an observational study. Indian J Transplant. 2022;16:216–9.
127. Lee CK, Merriam LT, Pearson JC, et al. Treating COVID-19: evolving approaches to evidence in a pandemic. Cell Rep Med. 2022;3(3): 100533.
128. Lamontagne F, Agarwal A, Rochwerg B, et al. A living WHO guideline on drugs for covid-19. BMJ. 2022. https://doi.org/10.1136/bmj.m3379.

129. World Health Organization (WHO). Therapeutics and COVID-19: living guideline. 2023. https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2023.1. Accessed 21 Jul 2023.
130. National Institute for Health and Care Excellence (NICE). COVID-19 rapid guideline: managing COVID-19. 2023. https://www.nice.org.uk/guidance/ng191. Accessed 21 Jul 2023.
131. National Institutes of Health (NIH). Coronavirus disease 2019 (COVID-19) treatment guidelines. 2023. www.covid19treatmentguidelines.nih.gov. Accessed 21 Jul 2023.
132. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. 2022. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 21 Jul 2023.
133. Qaseem A, Yost J, Etxeandia-Ikobaltzeta I, et al. Should remdesivir be used for the treatment of patients with COVID-19? Rapid, living practice points from the American College of Physicians (version 2, update alert 3). Ann Intern Med. 2022;175(5):W55–7.
134. Qaseem A, Yost J, Miller MC, et al. Outpatient treatment of confirmed COVID-19: living, rapid practice points from the American College of Physicians (version 1). Ann Intern Med. 2023;176(1):115–24.
135. Bartoletti M, Azap O, Barac A, et al. ESCMID COVID-19 living guidelines: drug treatment and clinical management. Clin Microbiol Infect. 2022;28(2):222–38.
136. Chalmers J, Crichton M, Goeminne P, et al. Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline. Eur Respir J. 2021;57(4):2100048.
137. Msemburi W, Karlinsky A, Knutson V, et al. The WHO estimates of excess mortality associated with the COVID-19 pandemic. Nature. 2023;613(7942):130–7.
138. Amstutz A, Speich B, Mentre F, et al. Effects of remdesivir in patients hospitalised with COVID-19: a systematic review and individual patient data meta-analysis of randomised controlled trials. Lancet Respir Med. 2023;11(5):453–64.
139. Ibekwe T, Ibekwe P, Orimadegun EA. Third force in the treatment of COVID-19: a systematic review and meta-analysis. Ann Med Surg (Lond). 2021;65: 102218.
140. Kaka AS, MacDonald R, Linskens EJ, et al. Major update 2: remdesivir for adults with COVID-19: a living systematic review and meta-analysis for the American College of Physicians practice points. Ann Intern Med. 2022;175(5):701–9.
141. Lee TC, Murthy S, Del Corpo O, et al. Remdesivir for the treatment of COVID-19: a systematic review and meta-analysis. Clin Microbiol Infect. 2022;28(9):1203–10.
142. Singh S, Khera D, Chugh A, et al. Efficacy and safety of remdesivir in COVID-19 caused by SARS-CoV-2: a systematic review and meta-analysis. BMJ Open. 2021;11(6): e048416.
143. Wilt TJ, Kaka AS, MacDonald R, et al. Remdesivir for adults with COVID-19: a living systematic review for American College of Physicians practice points. Ann Intern Med. 2021;174(2):209–20.
144. Kim PS, Read SW, Fauci AS. Therapy for early COVID-19: a critical need. JAMA. 2020;324(21):2149–50.
145. Gilead Sciences. CHMP adopts positive opinion to extend the use of Veklury® (remdesivir) to treat COVID-19 in people with severe renal impairment, including those on dialysis [media release]. 26 May 2023. https://www.gilead.com/.
146. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int. 2020;97(5):829–38.
147. Jager KJ, Kramer A, Chesnaye NC, et al. Results from the ERA-EDTA Registry indicate a high mortality due to COVID-19 in dialysis patients and kidney transplant recipients across Europe. Kidney Int. 2020;98(6):1540–8.
148. Budi DS, Oktavian P, Asmarawati TP, et al. Antiviral treatment in COVID-19 outpatients: a systematic review of randomized controlled trials. Acta Med Indones. 2022;54(4):540–55.
149. Pfizer. Paxlovid 150 mg + 100 mg film-coated tablets: EU summary of product characteristics. 2022. https://www.ema.europa.eu/en/documents/product-information/paxlovid-epar-product-information_en.pdf. Accessed 21 Jul 2023.
150. Pfizer. PAXLOVID-nirmatrelvir and ritonavir: US prescribing information. 2022. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7bdddfba-bd31-44cb-ba9e-23a4e17a4691. Accessed 21 Jul 2023.
151. Richards F, Kodjamanova P, Chen X, et al. Economic burden of COVID-19: a systematic review. Clinicoecon Outcomes Res. 2022;14:293–307.
152. Lau VI, Fowler R, Pinto R, et al. Cost-effectiveness of remdesivir plus usual care versus usual care alone for hospitalized patients with COVID-19: an economic evaluation as part of the Canadian Treatments for COVID-19 (CATCO) randomized clinical trial. CMAJ Open. 2022;10(3):E807–17.
153. Rezapour A, Behroozi Z, Nasirzadeh M, et al. Cost-effectiveness of remdesivir for the treatment of hospitalized patients with COVID-19: a systematic review. Infect Dis Poverty. 2023;12(1):39.
154. Subhi A, Shamy AME, Hussein SAM, et al. Use of anti-viral therapies in hospitalised COVID-19 patients in the United Arab Emirates: a cost-effectiveness and health-care resource use analysis. BMC Health Serv Res. 2023;23(1):383.
155. Barnieh L, Beckerman R, Jeyakumar S, et al. Remdesivir for hospitalized COVID-19 patients in the United States: optimization of health care resources. Infect Dis Ther. 2023;12(6):1655–65.
156. Whittington MD, Pearson SD, Rind DM, et al. The cost-effectiveness of remdesivir for hospitalized patients with COVID-19. Value Health. 2022;25(5):744–50.
157. Rafia R, Martyn-St James M, Harnan S, et al. A cost-effectiveness analysis of remdesivir for the treatment of hospitalized patients with COVID-19 in England and Wales. Value Health. 2022;25(5):761–9.