WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[CV001 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg of remdesivir.

After reconstitution, each vial contains 5 mg/mL of remdesivir solution.

Excipients with potential clinical effect

Each 100 mg dose contains approximately 333 mg of sodium. See section 4-4.

For the list of excipients, see section 6-1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

White to off white to yellow lyophilized cake or powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[CV001 trade name] is indicated for the treatment of non-severe COVID-19 (oxygen saturation over 90% and no signs of pneumonia or severe respiratory distress) in patients weighing at least 40 kg, who are at high risk of progressing to severe COVID-19.

A higher risk of progressing to severe COVID-19 may be associated with any of the following patient factors:

- age of 60 years or older
- BMI greater than 25 kg/m^2
- diabetes
- chronic lung disease (including asthma) or being a smoker
- chronic kidney disease
- immunosuppressive disease or immunosuppressive treatment
- cardiovascular disease or hypertension
- sickle cell disease
- neurodevelopmental disorders
- active cancer
- dependence on a medical technology device to manage a clinical condition.

Lack of vaccination against SARS-CoV-2 is an additional risk factor.

[CV001 trade name] may also be used for the treatment of severe COVID-19 in adults and children (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen.

The management of COVID-19 should follow the most recent authoritative guidelines, including those issued by WHO..

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

4.2 Posology and method of administration

Posology

It is advised that patients receiving remdesivir in an outpatient setting are monitored according to local medical practice. Treatment should be given under conditions where treatment of severe hypersensitivity reactions, including anaphylaxis, is possible (see section 4.4).

Dosing depends on age and body weight, and on whether patients have non-severe or severe COVID-19.

		Non-severe COVID-19*	**Severe COVID-19**
Adults and children weighing at least 40 kg	*Day 1*	200 mg	200 mg
	Day 2 onwards	100 mg daily for 2 days	100 mg daily for at least 4 but no more than 9 days
Children (at least 4 weeks old) weighing from 3 to less than 40 kg	*Day 1*	*Not applicable*	5 mg/kg
	Day 2 onwards	*Not applicable*	2.5 mg/kg daily for up to a total of 9 days
*Treatment should start as soon as possible after diagnosis of COVID-19 and within 7 days after onset of symptoms.			

Special populations

Elderly

No dose adjustment of remdesivir is required in patients older than 65 years.

Hepatic impairment

No dose adjustment of remdesivir is required in patients with mild, moderate and severe hepatic impairment (Child-Pugh Class A, B, C) (see section 5.2). However, safety data in patients with severe hepatic impairment are limited and only based on a single 100-mg dose.

Renal impairment

No dose adjustment of remdesivir is required in patients with renal impairment, including those on dialysis. However, safety data in patients with severe renal impairment and end-stage renal disease (ESRD) are limited (see section 4.4) and based on a 5-day treatment duration. Remdesivir can be given without regard to the timing of any dialysis (see section 5.2).

Method of administration

Remdesivir is only to be administered by intravenous infusion. For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

Recommended rate of infusion in patients weighing at least 40 kg

Infusion volume	**Infusion time**	**Rate of infusion**
250 mL	30 minutes	8.33 mL/minute
	60 minutes	4.17 mL/minute
	120 minutes	2.08 mL/minute
100 mL	30 minutes	3.33 mL/minute
	60 minutes	1.67 mL/minute

Infusion volume	Infusion time	Rate of infusion
	120 minutes	0.83 mL/minute

Recommended rate of infusion in patients weighing 3 to less than 40 kg

Infusion volume	Infusion time	Rate of infusion*
100 mL	30 minutes	3.33 mL/minute
	60 minutes	1.67 mL/minute
	120 minutes	0.83 mL/minute
50 mL	30 minutes	1.67 mL/minute
	60 minutes	0.83 mL/minute
	120 minutes	0.42 mL/minute
25 mL	30 minutes	0.83 mL/minute
	60 minutes	0.42 mL/minute
	120 minutes	0.21 mL/minute

* Rate of infusion may be adjusted based on total volume to be infused

[Text for section 6.6 – to be moved by person compiling the WHOPAR.]

Prepare solution for infusion under aseptic conditions and on the same day as administration.

Before administration, remdesivir must be reconstituted with water for injections and diluted in sodium chloride 9 mg/mL (0.9%) solution for injection as indicated below.

After infusion is complete, flush with at least 30 mL of sodium chloride 9 mg/mL.

Preparation of remdesivir solution for infusion

Reconstitution

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

- Reconstitute remdesivir powder for concentrate for solution for infusion by addition of 19 mL of sterile water for injections using a suitably sized syringe and needle per vial.
  - Discard the vial if a vacuum does not pull the sterile water for injections into the vial.
- Immediately shake the vial for 30 seconds.
- Allow the contents of the vial to settle for 2 to 3 minutes. A clear solution should result. The solution contains remdesivir 5 mg/mL. (If the powder has not completely dissolved shake again and allow to settle.)
- Inspect the vial to ensure the container closure is intact and the solution is free of particulate matter.
- Dilute immediately after reconstitution.

Dilution

It is recommended to administer immediately after dilution when possible.

<u>Adults and children weighing at least 40 kg</u>

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- Use a 250-mL bag of sodium chloride 9 mg/mL (0.9%) solution for infusion to dilute the reconstituted remdesivir solution. A 100-mL bag may be used for patients on severe fluid restriction (e.g. those with renal failure or acute respiratory distress syndrome).
- From the bag of sodium chloride 9 mg/mL solution for infusion, withdraw and discard 20 mL of the infusion fluid for each 100-mg dose of remdesivir to be added (i.e. discard 20 mL for 100-mg dose and 40 mL for 200-mg dose).

- Add to the infusion bag the contents of one vial (100 mg remdesivir in 20 mL) or two vials (200 mg remdesivir in 40 mL) of the reconstituted solution, as required.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- The prepared infusion solution is stable for 24 hours at room temperature (20 to 25°C) or 48 hours in the refrigerator (2 to 8°C).
- Before infusion, allow the remdesivir infusion solution to reach room temperature and inspect it for particulate matter and discoloration. Discard the solution if particles are present or if it is discoloured.
- Infuse the remdesivir infusion solution over 30 to 120 minutes (see section 4.2)

Children at least 4 weeks of age and weighing 3 to less than 40 kg

- Dilute the reconstituted remdesivir solution (5 mg/mL) to 1.25 mg/mL with 0.9% sodium chloride 9 mg/mL solution for injection.
- The volume of this diluted remdesivir solution needed to give the first dose (of 5 mg/kg) is 4 mL for each kg of body weight and the volume needed to give subsequent doses (of 2.5 mg/mL) is 2 mL for each kg of body weight.
- Before infusion, allow the remdesivir infusion solution to reach room temperature and inspect it for particulate matter and discoloration. Discard the solution if particles are present or if it is discoloured.
- Infuse the remdesivir infusion solution over 30 to 120 minutes (see section 4.2). Use a syringe driver if the infusion volume is less than 50 mL.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity including infusion-related and anaphylactic reactions

Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed during and after administration of remdesivir. Signs and symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnoea, wheezing, angioedema, rash, nausea, vomiting, sweating, and shivering.

Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. Monitor patients for hypersensitivity reactions during and after administration of remdesivir as clinically appropriate. Patients receiving remdesivir in an outpatient setting should be monitored after administration according to local medical practice. If signs and symptoms of a clinically significant hypersensitivity reaction occur, stop giving remdesivir immediately and begin appropriate treatment.

Renal impairment

As clinically appropriate, patients should have eGFR determined before starting remdesivir and while receiving it. Safety data from patients with severe renal impairment and end-stage renal disease given remdesivir in studies have been reported to be comparable to the known safety profile of remdesivir. However, there are limited safety data in this patient population. Therefore, taking the significant higher exposure of the metabolite GS-441524 into account, patients with severe renal impairment and end-stage renal disease should be closely monitored for adverse events during treatment with remdesivir (see section 5.2)

Immunocompromised patients

It is unclear if the treatment duration of 3 days is sufficient to clear the virus in immunocompromised patients with non-severe COVID-19, in whom prolonged viral shedding occurs. There is a potential risk of resistance development. Only limited data are available.

Excipients

This medicinal product contains approximately 333 mg sodium per 100 mg dose, equivalent to 16.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

The antiviral activity of remdesivir was antagonised by chloroquine in a dose-dependent manner when the two drugs were co-incubated at clinically relevant concentrations in HEp-2 cells infected with respiratory syncytial virus (RSV). Higher remdesivir EC_{50} values were observed with increasing concentrations of chloroquine. Increasing concentrations of chloroquine reduced formation of remdesivir triphosphate in A549-hACE2, HEp-2 and normal human bronchial epithelial cells.

Due to this antagonism observed in vitro, concomitant use of remdesivir with chloroquine or hydroxychloroquine is not recommended.

Pharmacokinetic interactions

Effects of other medicinal products on remdesivir

In vitro, remdesivir is a substrate for esterases in plasma and tissue, drug metabolising enzyme CYP3A4 and is a substrate for the OATP1B1 and P-glycoprotein (P-gp) transporters. GS-704277 (a metabolite of remdesivir) is a substrate for OATP1B1 and OATP1B3.

However, a drug-drug interaction study in which remdesivir was co-administered with ciclosporin (an inhibitor of OATP transporters and P-gp) and carbamazepine (a strong inducer of CYP3A4) confirmed that no dose adjustment of remdesivir is required when it is given with inhibitors or OATP1B1/OATO1B3 or with strong CYP3A4 or P-gp inducers.

Effects of remdesivir on other medicinal products

Remdesivir is not a clinically relevant *inhibitor* of CYP3A4, OATP1B1, and OATP1B3. In vitro, remdesivir is an inhibitor of UGT1A1, MATE1, OAT3, and OCT1; however no clinically significant drug interactions are expected with remdesivir and substrates of these enzymes or transporters.

Remdesivir is not a clinically relevant *inducer* of CYP3A4. Remdesivir induced CYP1A2 in vitro; however no clinically significant drug interaction is expected with remdesivir and CYP1A2 substrates.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

There is a limited amount of data from the use of remdesivir in pregnant women (fewer than 300 pregnancy outcomes). Most of the exposures (where pregnancy stage was reported) occurred in the second or third trimester, and available data do not indicate any risk.

Animal studies do not indicate direct or indirect reproductive toxicity at exposures of the major metabolite of remdesivir that were around human therapeutic exposures (see section 5.3).

Due to very limited experience, remdesivir should not be used during first trimester in pregnancy unless the clinical condition of the woman requires such treatment. Use in the second and third trimester of pregnancy may be considered.

Use of effective contraception during treatment should be considered in women of child-bearing potential..

Breast-feeding

Remdesivir and its major metabolite pass into breast milk in very small amounts after intravenous administration. No clinical effect on the infant is expected due to low breast milk transfer and poor oral bioavailability.

Women may therefore continue to breastfeed while receiving remdesivir, with appropriate monitoring of the infant.

Fertility

No human data on the effect of remdesivir on fertility are available. In male rats, there was no effect of remdesivir treatment on mating or fertility. In female rats, however, fertility was impaired (see section 5.3). The relevance for humans is unknown.

4.7 Effects on ability to drive and use machines

[CV001 trade name] is expected to have no significant influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reaction with [CV001 trade name] in healthy volunteers is increased transaminases. The most common adverse reaction in patients with COVID-19 is nausea.

Tabulated summary of adverse reactions

Adverse reactions to remdesivir are listed below by body system or organ. Frequencies are defined as follows: very common (at least 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1 in 1000), very rare (less than 1 in 10 000) or not known (frequency cannot be estimated from available data).

Immune system disorders	
rare	hypersensitivity
not known	anaphylactic reaction, anaphylactic shock
Nervous system disorders	
common	headache
Cardiac disorders	
not known	sinus bradycardia (usually normalised within 4 days of last remdesivir dose without additional treatment)
Gastrointestinal disorders	
common	nausea
Hepatobiliary disorders	
very common	transaminases increased
Skin and subcutaneous tissue disorders	
common	rash
Investigations	
very common	prothrombin time prolonged
Injury, poisoning and procedural complications	
rare	infusion-related reaction

Description of selected adverse reactions

Transaminases increased

In healthy volunteers given remdesivir in studies, increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST) or both were 1.25 to 2.5 times the upper limit of normal (ULN) in around 10% of subjects and 2.5 to 5 times ULN in 4%.

In clinical studies of patients with COVID-19, the incidence of increased transaminases was similar in patients treated with remdesivir compared to placebo or standard of care.

Prothrombin time prolonged

In a clinical study (NIAID ACTT-1) of patients with COVID-19, the incidence of prolonged prothrombin time or INR (predominantly less than 2 times the usual upper limit) was higher in subjects who received remdesivir compared to placebo, with no difference in the incidence of bleeding events between the two groups. In Study GS-US-540-9012, the incidence of increased prothrombin time or INR was similar in patients treated with remdesivir compared to placebo.

Patients with renal impairment

In Study GS-US-540-5912, 163 hospitalised patients with confirmed COVID-19 and acute kidney injury, chronic kidney disease or ESRD on haemodialysis received remdesivir for up to 5 days (see sections 4.4 and 5.2). Safety data from these patients were comparable to the known safety profile of remdesivir. In this same study, the incidence of increased prothrombin time or INR was higher in patients treated with remdesivir compared to placebo, with no difference in the incidence of bleeding events between the two groups (see section 5.1).

Paediatric population

The safety assessment of remdesivir in children 4 weeks of age and older and weighing at least 3 kg with COVID-19 is based on data from a Phase 2/3, open-label clinical trial (Study GS-US-540-5823) that enrolled 53 patients who were treated with remdesivir (see Section 5.1). The adverse reactions were consistent with those observed in clinical trials of remdesivir in adults.

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

There is no specific antidote for overdose with remdesivir. Treatment of overdose with remdesivir should consist of general supportive measures including monitoring vital signs and the patient's clinical status.

In one clinical pharmacology trial, remdesivir 600 mg as a single dose over 30 minutes, equivalent to 3 times the therapeutic loading dose of 200 mg, was administered to 60 healthy subjects. Nausea and/or vomiting (Grades 1-2) was reported for 33 (55%) subjects. One subject (2%) had increased AST and ALT (Grade 4) without elevation of bilirubin.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, direct acting antivirals, ATC code: J05AB16.

Mechanism of action

Remdesivir is an adenosine nucleotide prodrug that is metabolised within host cells to form the pharmacologically active nucleoside triphosphate metabolite. Remdesivir triphosphate acts as an analogue of adenosine triphosphate (ATP) and competes with the natural ATP substrate for incorporation into nascent

RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase, which results in delayed chain termination during replication of the viral RNA.

As an additional mechanism, remdesivir triphosphate can inhibit viral RNA synthesis following its incorporation into the template viral RNA as a result of read-through by the viral polymerase that may occur in the presence of higher nucleotide concentrations. When remdesivir nucleotide is present in the viral RNA template, the efficiency of incorporation of the complementary natural nucleotide is compromised, thereby inhibiting viral RNA synthesis.

Antiviral activity in vitro

Remdesivir exhibited in vitro activity against a clinical isolate of SARS-CoV-2 in primary human airway epithelial cells with a 50% effective concentration (EC_{50}) of 9.9 nM after 48 hours of treatment. Remdesivir inhibited the replication of SARS-CoV-2 in the continuous human lung epithelial cell lines Calu-3 and A549-hACE2 with EC_{50} values of 280 nM after 72 hours of treatment and 115 nM after 48 hours of treatment, respectively. The EC_{50} values of remdesivir against SARS-CoV-2 in Vero cells were 137 nM at 24 hours and 750 nM at 48 hours post-treatment.

Based on in vitro testing, remdesivir retained similar antiviral activity (EC_{50} fold change values below the in vitro susceptibility change cutoff of 2.8-fold) against clinical isolates of SARS-CoV-2 variants compared to an earlier lineage SARS-CoV-2 (lineage A) isolate, including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Epsilon (B.1.429), Zeta (P.2), Iota (B.1.526), Kappa (B.1.617.1), Lambda (C.37) and Omicron variants (including B.1.1.529/BA.1, BA.2, BA.2.12.1, BA.2.75, BA.4, BA.4.6, BA.5, BF.5, BF.7, BQ.1, BQ.1.1, CH.1.1, EG.1.2, EG.5.1, FL.22, XBB, XBB.1.5, XBB.1.16, XBB.2.3.2 and XBF). For these variants, the EC_{50} fold change values ranged between 0.2 to 2.3 compared to an earlier lineage SARS-CoV-2 (lineage A) isolate. Using the SARS-CoV-2 replicon system, remdesivir retained similar antiviral activity (EC_{50} fold change values below the in vitro susceptibility change cutoff of 2.5-fold) against Omicron subvariants BA.2.86 and XBB.1.9.2 compared to the wildtype reference replicon (lineage B).

The antiviral activity of remdesivir was antagonised in vitro by chloroquine (see section 4.5).

Resistance

In cell culture

SARS-CoV-2 isolates with reduced susceptibility to remdesivir have been selected in cell culture. In one selection with GS-441524, the parent nucleoside of remdesivir, virus pools emerged expressing combinations of amino acid substitutions at V166A, N198S, S759A, V792I, C799F, and C799R in the viral RNA-dependent RNA polymerase, conferring EC_{50} fold-changes of 2.7 up to 10.4. When individually introduced into a wild-type recombinant virus by site-directed mutagenesis, 1.7- to 3.5- fold reduced susceptibility to remdesivir was observed. In a second selection with remdesivir using a SARS-CoV-2 isolate containing the P323L substitution in the viral polymerase, a single amino acid substitution at V166L emerged. Recombinant viruses with substitutions at P323L alone or P323L+V166L in combination exhibited 1.3- and 1.5-fold changes in remdesivir susceptibility, respectively.

Cell culture resistance profiling of remdesivir using the rodent CoV murine hepatitis virus identified two substitutions (F476L and V553L) in the viral RNA-dependent RNA polymerase at residues conserved across CoVs that conferred 5.6-fold reduced susceptibility to remdesivir. Introduction of the corresponding substitutions (F480L and V557L) into SARS-CoV resulted in 6-fold reduced susceptibility to remdesivir in cell culture and attenuated SARS-CoV pathogenesis in a mouse model. When individually introduced into a SARS-CoV-2 recombinant virus, the corresponding substitutions at F480L and V557L each conferred 2-fold reduced susceptibility to remdesivir.

In clinical trials

In NIAID ACTT-1 Study (CO-US-540-5776), among 61 patients with baseline and post-baseline sequencing data available, the rate of emerging substitutions in the viral RNA-dependent RNA polymerase was similar in patients treated with remdesivir compared to placebo. In 2 patients treated with remdesivir, substitutions in the RNA-dependent RNA polymerase previously identified in resistance selection experiments (V792I or

C799F) and associated with low fold change in remdesivir susceptibility (≤3.4-fold) were observed. No other RNA-dependent RNA polymerase substitutions observed in patients treated with remdesivir were associated with resistance to remdesivir.

In Study GS-US-540-5773, among 19 patients treated with remdesivir who had baseline and postbaseline sequencing data available, substitutions in the viral RNA-dependent RNA polymerase (nsp12) were observed in 4 patients. The substitutions T76I, A526V, A554V and C697F were not associated with resistance to remdesivir (≤ 1.45-fold change in susceptibility). The effect of substitution E665K on susceptibility to remdesivir could not be determined due to lack of replication.

In GS-US-540-9012 Study, among 244 patients with baseline and post-baseline sequencing data available, the rate of emerging substitutions in the viral RNA-dependent RNA polymerase was similar in patients treated with remdesivir compared to placebo. In one patient treated with remdesivir, one substitution in the RNA-dependent RNA polymerase (A376V) emerged and was associated with a decrease in remdesivir susceptibility in vitro (12.6-fold). No other substitutions in the RNA-dependent RNA polymerase or other proteins of the replication-transcription complex observed in patients treated with remdesivir were associated with resistance to remdesivir.

In Study GS-US-540-5912, among 60 patients with baseline and post-baseline sequencing data available, substitutions in the viral RNA-dependent RNA polymerase emerged in 8 patients treated with remdesivir. In 4 patients treated with remdesivir, substitutions in the RNA-dependent RNA polymerase (M794I, C799F, or E136V) emerged and were associated with reduced susceptibility to remdesivir in vitro (≤3.5-fold). No other substitutions in the RNA-dependent RNA polymerase detected in patients treated with remdesivir were associated with resistance to remdesivir.

In Study GS-US-540-5823, among patients with baseline and post-baseline sequencing data available, substitutions in the viral RNA-dependent RNA polymerase (A656P and G670V) were observed in one of 23 patients treated with remdesivir. The substitutions observed have not been associated with resistance to remdesivir.

Clinical efficacy and safety

Clinical trials

A randomised, double-blind, placebo-controlled clinical trial (*NIAID ACTT-1 Study, CO-US-540-5776*) evaluated COVID-19 treatment with remdesivir 200 mg once daily for 1 day followed by remdesivir 100 mg once daily for up to 9 days (for a total of up to 10 days of intravenously administered therapy).

The trial enrolled 1062 hospitalised patients: 159 (15%) patients with mild/moderate COVID-19 (15% in both treatment groups) and 903 (85%) patients with severe disease (85% in both treatment groups). Mild/moderate disease was defined as SpO2 > 94% and respiratory rate < 24 breaths/minute without supplemental oxygen; severe disease was defined as SpO2 ≤ 94% on room air, a respiratory rate ≥ 24 breaths/minute, and an oxygen requirement, or a requirement for mechanical ventilation. A total of 285 patients (26.8%) (n=131 received remdesivir) were on mechanical ventilation/extracorporeal membrane oxygenation (ECMO).

Patients were randomised 1:1, stratified by disease severity at enrolment, to receive remdesivir (n=541) or placebo (n=521), plus standard of care. The baseline mean age was 59 years and 36% of patients were aged 65 or older. Sixty-four percent were male, 53% were White, 21% were Black, 13% were Asian. The most common comorbidities were hypertension (51%), obesity (45%) and type 2 diabetes mellitus (31%); the distribution of comorbidities was similar between the two treatment groups. Approximately 38.4% (208/541) of the patients received a 10-day treatment course with remdesivir.

The primary clinical endpoint was time to recovery within 29 days after randomisation, defined as either discharged from hospital (with or without limitations of activity and with or without home oxygen requirements) or hospitalised but not requiring supplemental oxygen and no longer requiring ongoing medical care.

The median time to recovery was 10 days in the remdesivir group compared to 15 days in the placebo group (recovery rate ratio 1.29; [95% CI 1.12 to 1.49], p < 0.001). No difference in time to recovery was seen in the patients with mild-moderate disease at enrolment: the median time to recovery was 5 days in the remdesivir and 7 days in the placebo groups (recovery rate ratio 1.10; [95% CI 0.8 to 1.53]. Among patients with severe disease at enrolment (n=903), the median time to recovery was 12 days in the remdesivir group compared to 19 days in the placebo group (recovery rate ratio, 1.34; [95% CI 1.14 to 1.58]; p < 0.001).

The 29-day mortality in the overall population was 11.6% for the remdesivir group vs 15.4% for the placebo group (hazard ratio, 0.73; [95% CI 0.52 to 1.03]; p=0.07).

A randomised, open-label multi-centre clinical trial (*GS-US-540-5773*) of patients at least 12 years of age with confirmed SARS-CoV-2 infection, oxygen saturation of ≤ 94% on room air, and radiological evidence of pneumonia compared 200 patients who received remdesivir for 5 days with 197 patients who received remdesivir for 10 days. All patients received 200 mg of remdesivir on Day 1 and 100 mg once daily on subsequent days, plus standard of care. The primary endpoint was clinical status on Day 14 assessed on a 7-point ordinal scale ranging from hospital discharge to increasing levels of oxygen and ventilatory support to death.

The odds of improvement at Day 14 for patients randomised to a 10-day course of remdesivir compared with those randomised to a 5-day course was 0.67 (odds ratio); [95% CI 0.46 to 0.98]. Statistically significant imbalances in baseline clinical status were observed in this study. After adjusting for between-group differences at baseline, the odds of improvement at Day 14 was 0.75 (odds ratio); [95% CI 0.51 to 1.12]. In addition, there were no statistically significant differences in recovery rates or mortality rates in the 5-day and 10-day groups once adjusted for between group differences at baseline. All-cause 28-day mortality was 12% vs 14% in the 5- and 10-day treatment groups, respectively.

In *Study GS-US-540-9012* the efficacy of remdesivir in the treatment of COVID-19 was evaluated in an outpatient setting in patients at increased risk for disease progression. This was a randomised, double-blind, placebo-controlled, multi-centre clinical trial in 562 adult patients with confirmed COVID-19 who had symptom onset within the previous 7 days and at least one of the risk factors for disease progression to hospitalisation. Vaccinated patients were excluded from the study. Post-hoc exploratory analysis of optional biomarker samples showed 14.8% of patients were serological 13 positive at baseline and 37.7% were serological negative (47.5% did not consent to optional biomarker collection).

Patients treated with remdesivir received 200 mg on Day 1 and 100 mg once daily on subsequent days for a total of 3 days of intravenously administered therapy. Patients were 11andomised in a 1:1 manner, stratified by residence in a skilled nursing facility (yes/no), age (< 60 vs ≥ 60 years), and region (US vs ex-US) to receive remdesivir (n=279) or placebo (n=283), plus standard of care.

At baseline, mean age was 50 years (with 30% of patients aged 60 or older); 52% were male, median body mass index was 30.7 kg/m^2. The most common comorbidities were diabetes mellitus (62%), obesity (56%), and hypertension (48%). Median (Q1, Q3) duration of symptoms prior to treatment was 5 (3,6) days; median viral load was 6.3 log_{10} copies/mL at baseline. The baseline demographics and disease characteristics were balanced across the remdesivir and placebo treatment groups.

The primary endpoint was the proportion of patients with COVID-19 related hospitalisation (defined as at least 24 hours of acute care) or all-cause 28-day mortality. These events occurred in 2 (0.7%) patients treated with remdesivir compared to 15 (5.3%) given placebo. This translated into an 87% reduction in COVID-19-related hospitalisation or all-cause mortality compared to placebo (hazard ratio, 0.134 [95% CI, 0.031 to 0.586]; p=0.0076). The absolute risk reduction was 4.6% (95% CI, 1.8% to 7.5%). No deaths occurred by Day 28.

Study GS-US-540-5823 is an ongoing single-arm, open-label study to assess the pharmacokinetics and safety of remdesivir in paediatric patients at least 28 days of age and weighing at least 3 kg with COVID-19 (n=53). A descriptive analysis has been carried out but should be interpreted with caution as efficacy endpoints are secondary. Patients weighing ≥ 40 kg received 200 mg of remdesivir on Day 1 followed by remdesivir 100 mg once daily on subsequent days (i.e. the adult dose); patients weighing ≥ 3 kg to < 40 kg received

remdesivir 5 mg/kg on Day 1 followed by remdesivir 2.5 mg/kg once daily on subsequent days. Median (range) exposure to remdesivir was 5 (1, 10) days.

Median age at baseline was 7 years (range: 0.1 to 17 years); 57% were female; median weight was 24.6 kg (range: 4 kg to 192 kg). A total of 19 patients (37%) were obese (BMI-for-age ≥ 95th percentile. A total of 12 patients (23%) were on invasive mechanical ventilation (score of 2 in a 7- point ordinal scale), 18 (34%) were on non-invasive ventilation or high-flow oxygen (score of 3); 10 (19%) were on low-flow oxygen (score of 4); and 13 (25%) were on room air (score of 5), at baseline. The overall median (Q1, Q3) duration of symptoms and hospitalisation prior to first dose of remdesivir was 5 (3, 7) days and 1 (1, 3) day, respectively.

In the overall population of the study, the median (Q1, Q3) change from baseline in clinical status (assessed on a 7-point ordinal scale ranging from death [score of 1] to hospital discharge [score of 7]) was +2.0 (1.0, 4.0) points on Day 10. Among those with an ordinal score of ≤ 5 points at baseline, the proportion who had a ≥ 2-point improvement in clinical status on Day 10 was 75.0% (39/52); median (Q1, Q3) time to recovery was 7 (5, 16) days. Overall, 60% of patients were discharged by Day 10. Most patients (92%; 49/53) received at least 1 concomitant medication other than remdesivir for the treatment of COVID-19 including immune modulator and anti-inflammatory agents. Three patients died during the study.

QT interval

Current non-clinical and clinical data do not suggest a risk of QT prolongation, but QT prolongation has not been fully evaluated in humans.

5.2 Pharmacokinetic properties

Pharmacokinetics of remdesivir

<table>
<tr><td>General</td><td>The pharmacokinetic properties of remdesivir have been investigated in healthy volunteers and patients with COVID-19.</td></tr>
<tr><td colspan="2">Absorption</td></tr>
<tr><td>Absorption</td><td>Following intravenous administration of remdesivir adult dosage regimen in healthy adults, peak plasma concentration occurred at end of infusion, regardless of dose level, and declined rapidly thereafter. Peak plasma concentrations of GS-441524 occurred 1.5 to 2.0 hours after the start of a 30-minute infusion.

In adults with COVID-19, the following multiple-dose PK parameters have been reported following administration of remdesivir 100 mg as a 30-minute infusion for 3 days:
<table>
<tr><th></th><th>Remdesivir</th><th>GS-441524</th><th>GS-704277</th></tr>
<tr><td>C_{max} (ng/mL)</td><td>2700 (2440, 2990)</td><td>143 (135, 152)</td><td>195 (180, 218)</td></tr>
<tr><td>AUC_{tau} (ng·h/mL)</td><td>1710 (1480,2580)</td><td>2410 (2550, 2580)</td><td>392 (348, 442)</td></tr>
<tr><td>C_{tau} (ng/mL)</td><td>ND</td><td>61.5 (56.5, 66.8)</td><td>ND</td></tr>
</table>
Values are given as geometric mean estimates followed by (95% CI)
ND=not detectable (at 24 hours post-dose)</td></tr>
<tr><td colspan="2">Distribution</td></tr>
<tr><td>Volume of distribution (mean ± SD)</td><td>Not available</td></tr>
<tr><td>Plasma protein binding (ex-vivo data)</td><td>Approximately 93%; free fraction 6.4–7.4%

The binding is independent of drug concentration over the range of 1 to 10 μM, with no evidence for saturation of remdesivir binding.</td></tr>
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Distribution	After a single 150-mg dose of [^{14}C]-remdesivir, blood to plasma ratio of [^{14}C]-radioactivity was approximately 0.68 at 15 minutes from start of infusion, increased over time reaching a ratio of 1.0 at 5 hours, indicating differential distribution of remdesivir and its metabolites to plasma or cellular components of blood.
Metabolism	
Bio-transformation	The metabolic activation pathway involves hydrolysis by esterases, which leads to the formation of the intermediate metabolite, GS-704277. Phosphoramidate cleavage followed by phosphorylation forms the active triphosphate, GS-443902. Dephosphorylation of all phosphorylated metabolites can result in the formation of nucleoside metabolite GS-441524 that itself is not efficiently re-phosphorylated. Decyanation of remdesivir and/or its metabolites, followed by subsequent rhodanese-mediated conversion, generates thiocyanate anion at levels significantly below endogenous levels in human plasma.
Active metabolite(s)	nucleoside analog triphosphate GS-443902 (formed intracellularly)
Elimination	
Elimination half life	Approximately 1 hour
Mean systemic clearance (Cl/F)	Not available
% of dose excreted in urine	Following a single 150-mg IV dose of [^{14}C]-remdesivir, 74% of the dose was recovered in urine, the majority as GS-441524 (49%) and 10% as remdesivir
% of dose excreted in faeces	Following a single 150-mg IV dose of [^{14}C]-remdesivir: 18%
Drug interactions (*in vitro*)	
Transporters	Inhibition of OATP1B1and OATP1B3; no data available for OAT1, OAT3 or OCT2 inhibition.
Metabolising Enzymes	Inhibition of CYP3A4; at physiologically relevant concentrations (steady-state), remdesivir or its metabolites GS-441524 and GS-704277 did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6 in vitro. Remdesivir may, however, transiently inhibit CYP2B6, 2C8, 2C9 and 2D6 on the first day of administration. The clinical relevance of this inhibition is not known. The potential for time-dependent inhibition of CYP450 enzymes by remdesivir was not studied. Induction of CYP1A2 and potentially CYP3A4, but not CYP2B6. No clinically relevant inhibition of UGT1A1, 1A3, 1A4, 1A6, 1A9 or 2B7.

Pharmacokinetics in special populations

Gender, race and age

Based on gender, race and age, pharmacokinetic differences on the exposures of remdesivir were evaluated using population pharmacokinetic analysis. Gender and race did not affect the pharmacokinetics of remdesivir and its metabolites (GS-704277 and GS-441524). Pharmacokinetic exposures of the GS-441524 metabolite were modestly increased in hospitalised COVID-19 patients 60 or more years of age, but no dose adjustment is needed in these patients.

Pregnancy

In CO-US-540-5961 (IMPAACT 2032) study, mean exposures (AUC_{tau}, C_{max}, and C_{tau}) of remdesivir and its metabolites (GS-441524 and GS-704277) were comparable between pregnant and non-pregnant women of child-bearing potential.

Children

Population pharmacokinetic models for remdesivir and its circulating metabolites (GS-704277 and GS-441524), developed using pooled data from studies in healthy subjects and in adult and paediatric patients with COVID-19, were used to predict pharmacokinetic exposures in 50 paediatric patients aged ≥ 28 days to < 18 years and weighing ≥ 3 kg (Study GS-US-540-5823). Geometric mean exposures (AUC_{tau}, C_{max} and C_{tau}) for these patients at the doses administered were higher for remdesivir (44% to 147%), GS-441524 (-21% to 25%), and GS-704277 (7% to 91%) as compared to those in adult hospitalised patients with COVID-19 (see table). The increases were not considered clinically significant.

Renal impairment

The pharmacokinetics of remdesivir and its metabolites (GS-441524 and GS-704277) and the excipient SBECD were evaluated in healthy subjects, those with mild (eGFR 60–89 mL/minute), moderate (eGFR 30-59 mL/minute), severe (eGFR 15-29 mL/minute) renal impairment, or with ESRD (eGFR <15 mL/minute) on haemodialysis or not on haemodialysis following a single dose of up to 100 mg of remdesivir; and in a Phase 3 study in COVID-19 patients with severely reduced kidney function (eGFR <30 mL/minute) receiving remdesivir 200 mg on Day 1 followed by 100 mg from Day 2 to Day 5. Pharmacokinetic exposures of remdesivir were not affected by renal function or timing of remdesivir administration around dialysis. Exposures of GS-704277, GS-441524, and SBECD were up to 2.8-fold, 7.9-fold and 26-fold higher, respectively, in those with renal impairment than those with normal renal function which is not considered clinically significant based on limited available safety data. No dose adjustment of remdesivir is required for patients with renal impairment, including those on dialysis.

Hepatic impairment

The pharmacokinetics of remdesivir and its metabolites (GS-441524 and GS-704277) were evaluated in healthy subjects and those with moderate or severe hepatic impairment (Child-Pugh Class B or C) following a single dose of 100 mg of remdesivir. Relative to subjects with normal hepatic function, mean exposures (AUC_{inf}, C_{max}) of remdesivir and GS-704277 were comparable in moderate hepatic impairment and up to 2.4-fold higher in severe hepatic impairment; the increase was not considered clinically significant.

Hospitalisation

Pharmacokinetic exposures for remdesivir in hospitalised patients with severe COVID-19 pneumonia were generally within the range of the exposures in non-hospitalised patients. The GS-704277 and GS-441524 metabolite levels were modestly increased.

5.3 Preclinical safety data

Toxicology

Following intravenous administration (slow bolus) of remdesivir to rhesus monkeys and rats, severe renal toxicity occurred after short treatment durations. In male rhesus monkeys, dosage levels of 5, 10, and 20 mg/kg/day for 7 days all resulted in increased mean urea nitrogen and increased mean creatinine, renal tubular atrophy, and basophilia and casts; death occurred in one animal given 20 mg/kg/day. In rats, dosage levels of more than 3 mg/kg/day for up to 4 weeks resulted in findings indicative of kidney injury and/or dysfunction. Systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) were 0.1 times (monkeys at 5 mg/kg/day) and 0.3 times (rats at 3 mg/kg/day) the exposure in humans following intravenous administration at the recommended human dose (RHD).

Carcinogenesis

Long-term animal studies to evaluate the carcinogenic potential of remdesivir have not been performed.

Mutagenesis

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

Reproductive toxicity

In female rats, decreases in corpora lutea, numbers of implantation sites, and viable embryos, were seen when remdesivir was administered intravenously daily at a systemically toxic dose (10 mg/kg/day) 14 days prior to mating and during conception; exposures of the predominant circulating metabolite (GS-441524) were 1.3 times the exposure in humans at the RHD. There were no effects on female reproductive performance (mating, fertility, and conception) at this dose level.

In rats and rabbits, remdesivir demonstrated no adverse effect on embryofetal development when administered to pregnant animals at systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) that were up to 4 times the exposure in humans at the RHD.

In rats, there were no adverse effects on pre- and post-natal development at systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) that were similar to the exposure in humans at the RHD.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Betadex sulfobutyl ether sodium

6.2 Incompatibilities

This medicinal product must not be mixed or administered simultaneously with other medicinal products in the same dedicated line except those mentioned in section 6.6.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C until time of use. Do not freeze.

After reconstitution, vials can be stored up to 4 hours at 20°C to 25°C. Excursions allowed between 15°C and 30°C or 24 hours in the refrigerator at 2°C to 8°C.

6.5 Nature and contents of container

The powder for injection is filled into a 30mL clear tubular glass vial (USP Type I). The filled vial is closed with a grey bromobutyl rubber stopper with a flip off aluminium seal.

Available in packs of 6 x 1 vials.

6.6 Special precautions for disposal and other handling

Preparation of remdesivir solution for infusion

Prepare solution for infusion under aseptic conditions and on the same day as administration.

Before administration, remdesivir must be reconstituted with water for injections and diluted in sodium chloride 9 mg/mL (0.9%) solution for injection as indicated below.

After infusion is complete, flush with at least 30 mL of sodium chloride 9 mg/mL.

Reconstitution

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

- Reconstitute remdesivir powder for concentrate for solution for infusion by addition of 19 mL of sterile water for injections using a suitably sized syringe and needle per vial.
  - Discard the vial if a vacuum does not pull the sterile water for injections into the vial.
- Immediately shake the vial for 30 seconds.
- Allow the contents of the vial to settle for 2 to 3 minutes. A clear solution should result. The solution contains remdesivir 5 mg/mL. (If the powder has not completely dissolved shake again and allow to settle.)
- Inspect the vial to ensure the container closure is intact and the solution is free of particulate matter.
- Dilute immediately after reconstitution.

Dilution

It is recommended to administer immediately after dilution when possible.

Adults and children weighing at least 40 kg

- Use a 250-mL bag of sodium chloride 9 mg/mL (0.9%) solution for infusion to dilute the reconstituted remdesivir solution. A 100-mL bag may be used for patients on severe fluid restriction (e.g. those with renal failure or acute respiratory distress syndrome).
- From the bag of sodium chloride 9 mg/mL solution for infusion, withdraw and discard 20 mL of the infusion fluid for each 100-mg dose of remdesivir to be added (i.e. discard 20 mL for 100-mg dose and 40 mL for 200-mg dose).
- Add to the infusion bag the contents of one vial (100 mg remdesivir in 20 mL) or two vials (200 mg remdesivir in 40 mL) of the reconstituted solution, as required.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- The prepared infusion solution is stable for 24 hours at room temperature (20 to 25°C) or 48 hours in the refrigerator (2 to 8°C).
- Before infusion, allow the remdesivir infusion solution to reach room temperature and inspect it for particulate matter and discoloration. Discard the solution if particles are present or if it is discoloured.
- Infuse the remdesivir infusion solution over 30 to 120 minutes (see section 4.2)

Children at least 4 weeks of age and weighing 3 to less than 40 kg

- Dilute the reconstituted remdesivir solution (5 mg/mL) to 1.25 mg/mL with 0.9% sodium chloride 9 mg/mL solution for injection.
- The volume of this diluted remdesivir solution needed to give the first dose (of 5 mg/kg) is 4 mL for each kg of body weight and the volume needed to give subsequent doses (of 2.5 mg/mL) is 2 mL for each kg of body weight.
- Before infusion, allow the remdesivir infusion solution to reach room temperature and inspect it for particulate matter and discoloration. Discard the solution if particles are present or if it is discoloured.
- Infuse the remdesivir infusion solution over 30 to 120 minutes (see section 4.2). Use a syringe driver if the infusion volume is less than 50 mL.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

CV001

9. DATE OF PREQUALIFICATION

14 May 2025

10. DATE OF REVISION OF THE TEXT

May 2025

References

General reference sources for this SmPC include:

Therapeutics and COVID-19: Living guideline, 10 November 2023. Geneva: World Health Organization; 2022 (https://iris.who.int/bitstream/handle/10665/373975/WHO-2019-nCoV-therapeutics-2023.2-eng.pdf, accessed 10 March 2024)

National Institutes of Health. Therapeutic management of hospitalized children with COVID-19 (updated 29 Feb 2024). Maryland: NIH; 2024 (https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-children/hospitalized-children-therapeutic-management, accessed 10 March 2024).

Veklury 100 mg powder for concentrate for solution for infusion: summary of product characteristics. European Medicines Agency; 5 December 2023 (https://www.ema.europa.eu/en/documents/product-information/veklury-epar-product-information_en.pdf, accessed 10 March 2024)

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National Institutes of Health. Remdesivir (last rev. 15 Feb 2024). Drug and Lactation Database [LactMed]. Maryland: NIH; 2024 (https://www.ncbi.nlm.nih.gov/books/NBK556881, accessed 10 March 2024)

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products