swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Veklury®

International non-proprietary name:	remdesivir
Pharmaceutical form:	powder for concentrate for solution for infusion
Dosage strength(s):	100 mg
Route(s) of administration:	intravenous use
Marketing authorisation holder:	Gilead Sciences Switzerland Sàrl
Marketing authorisation no.:	68026
Decision and decision date:	extension of therapeutic indication approved on 19 December 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
COVID-19	Coronavirus disease 2019
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved indication in accordance with Article 23 TPO.

2.2 Indication and dosage

2.2.1 Requested indication

Treatment of coronavirus disease 2019 (COVID-19) in paediatric patients weighing at least 1.5 kg with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment), or who do not require supplemental oxygen or hospitalisation for COVID-19 and who are at increased risk of developing a severe COVID-19 course.

2.2.2 Approved indication

Treatment of coronavirus disease 2019 (COVID-19) in paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment), or who do not require supplemental oxygen or hospitalisation for COVID-19 and who are at increased risk of developing a severe COVID-19 course.

2.2.3 Requested dosage

Summary of the requested standard dosage:

a) Paediatric patients weighing at least 1.5 kg with pneumonia requiring supplemental oxygen:
2.5 mg/kg single loading dose on day 1 and 1.25 mg/kg once daily on day 2 and onwards up for a total of 10 days.

b) Paediatric patients weighing at least 1.5 kg who do not require supplemental oxygen or hospitalisation for COVID-19 and who are at increased risk of developing a severe COVID-19 course:

   i. Paediatric patients at least 4 weeks old (weighing at least 3 kg but less than 40 kg)
   5 mg/kg single loading dose on day 1 and 2.5 mg/kg once daily on day 2 and onwards for 3 days, starting as soon as possible after diagnosis of COVID-19 and within 7 days of the onset of symptoms.

   ii. Paediatric patients less than 4 weeks of age and weighing less than 3 kg
   2.5 mg/kg single loading dose on day 1 and 1.25 mg/kg once daily on day 2 and onwards for 3 days, starting as soon as possible after diagnosis of COVID-19 and within 7 days of the onset of symptoms.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	23 May 2024
Formal control completed	30 May 2024
List of Questions (LoQ)	1 October 2024
Response to LoQ	22 December 2024
Second List of Questions (LoQ)	13 March 2025
Response to Second LoQ	1 June 2025
Preliminary decision	19 September 2025
Response to preliminary decision	19 October 2025
Final decision	19 December 2025
Decision	approval

3 Medical context

The evaluation of the clinical (pharmacology) data for this application has been carried out in reliance on previous regulatory decisions by the EMA and the FDA. The available assessment reports and corresponding product information from these authorities were used as a basis for the clinical (pharmacology) evaluation.

4 Nonclinical aspects

4.1 Nonclinical conclusions

Nonclinical safety studies for remdesivir were previously reviewed in the context of the original marketing authorisation. No non-clinical data were submitted to support the requested indication extension. This can be accepted as there are no changes to the posology and route of administration, and the new submission is based on an analysis of human studies of GS-US-540-5823 and on population PK modelling and simulation studies to evaluate the efficacy and safety of Veklury in patients with COVID-19 aged 0 days to 18 years.
Efficacy for the proposed indication will be clinically evaluated.

Based on the ERA, the extension of the indication will not pose a risk to the environment.

5 Clinical aspects

The evaluation of the clinical (pharmacology) data for this application has been carried out in reliance on previous regulatory decisions by the EMA and the FDA. The available assessment reports and corresponding product information from these authorities were used as a basis for the clinical (pharmacology) evaluation.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Veklury was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

Veklury®

Composition

Veklury 100 mg powder for concentrate for solution for infusion

Active substances

Remdesivir

Excipients

Betadex sulfobutyl ether sodium, hydrochloric acid (to adjust pH), sodium hydroxide (to adjust pH).

A 100 mg Veklury dose of powder for concentrate for solution for infusion contains approximately 211.8 mg sodium and 3 g betadex sulfobutyl ether sodium.

Pharmaceutical form and active substance quantity per unit

Powder for concentrate for solution for intravenous infusion (powder for concentrate).
White to off-white to yellow powder.
Each vial contains 100 mg of remdesivir. After reconstitution, each vial contains 5 mg/ml of remdesivir solution.

Indications/Uses

Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg):

- with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment)
- who do not require supplemental oxygen or hospitalisation for COVID-19 and who are at increased risk of developing a severe COVID-19 course

(see “Properties/Effects”).

Dosage/Administration

Veklury should be used under conditions where treatment of severe hypersensitivity reactions, including anaphylaxis and anaphylactic shock, is possible. Patients should be monitored when receiving Veklury (see section “Warnings and precautions”).

Treatment should be intiated as soon as possible after a positive viral test for SARS-CoV-2 (see “Properties/Effects”).

Table 1: Recommended dose of Veklury in adults and paediatric patients

	Given by intravenous infusion over 30 to 120 min		
	Adults	**Paediatric patients (weighing at least 40 kg)**	**Paediatric patients at least 4 weeks old (weighing at least 3 kg but less than 40 kg)**
Day 1 (single loading dose)	200 mg	200 mg	5 mg/kg
Day 2 and onwards (once daily)	100 mg	100 mg	2.5 mg/kg

Table 2: Treatment duration

	Adults	**Paediatric patients (weighing at least 40 kg)**	**Paediatric patients at least 4 weeks old (weighing at least 3 kg but less than 40 kg)**
Patients with pneumonia and requiring supplemental oxygen	Daily for at least 5 days and not more than 10 days.	Daily for at least 5 days and not more than 10 days.	Daily for at least 5 days and not more than 10 days.
Patients who do not require supplemental oxygen or hospitalisation for COVID-19 and who are at increased risk of developing a severe COVID-19 course	Daily for 3 days,	Daily for 3 days	Daily for 3 days

Special dosage instructions

Patients with impaired hepatic function

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

Patients with impaired renal function

No dose adjustment of remdesivir is required in patients with renal impairment, including those on dialysis (see “Pharmacokinetics”). However, safety data in patients with severe renal impairment and end stage renal disease (ESRD) are limited (see “Warnings and precautions”) and based on a 5-day

treatment duration. The timing of administration of remdesivir is without regard to dialysis (see “Pharmacokinetics”).

Elderly patients

No dose adjustment of remdesivir is required in patients over the age of 65 years (see “Properties/Effect” and “Pharmacokinetics”).

Paediatric patients

The use of remdesivir in children is based on achieving similar exposures that have been shown to be effective in adults, and is further supported by results from a paediatric study in children from 4 weeks of age and with a body weight of at least 3 kg (see “Pharmacokinetics” and “Properties/Effects”). There are only limited data on the use of remdesivir in children under 4 weeks of age, and no dosage recommendation can be given. The currently available data are described in the sections “Properties/Effects” and “Pharmacokinetics”.

Mode of administration

For intravenous infusion use.

Veklury is for administration by intravenous infusion after reconstitution and further dilution.

It must not be given as an intramuscular (IM) injection.

For instructions on reconstitution and dilution of the medicinal product before administration, see “Instructions for handling”.

Table 3: Recommended rate of infusion for reconstituted and diluted Veklury powder for concentrate for solution for infusion in adults and paediatric patients weighing at least 40 kg

Infusion Bag Volume	Infusion Time	Rate of Infusion
250 ml	30 min	8.33 ml/min
	60 min	4.17 ml/min
	120 min	2.08 ml/min
100 ml	30 min	3.33 ml/min
	60 min	1.67 ml/min
	120 min	0.83 ml/min

Table 4: Recommended rate of infusion for reconstituted and diluted Veklury powder for concentrate for solution for infusion in paediatric patients at least 4 weeks of age and weighing at least 3 kg but less than 40 kg

Infusion Bag Volume	Infusion Time	Rate of Infusion[a]
100 ml	30 min	3.33 ml/min
	60 min	1.67 ml/min
	120 min	0.83 ml/min
50 ml	30 min	1.67 ml/min
	60 min	0.83 ml/min
	120 min	0.42 ml/min

Infusion Bag Volume	Infusion Time	Rate of Infusion[a]
25 ml	30 min	0.83 ml/min
	60 min	0.42 ml/min
	120 min	0.21 ml/min

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

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

Hypersensitivity including infusion-related and anaphylactic reactions

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

Transaminase elevations

Safety data in patients with severe hepatic impairment are limited and only based on a single 100 mg dose administration.
An increase in transaminase elevations was observed in clinical studies with remdesivir in healthy volunteers and in patients with COVID-19 (see “Undesirable effects”).
Liver function should be monitored while receiving remdesivir as clinically appropriate:

- Consider discontinuing remdesivir if ALT levels increase to greater than 10 times the upper limit of normal.
- Discontinue remdesivir if ALT elevation is accompanied by signs or symptoms of liver inflammation.

Renal Impairment

As clinically appropriate, patients should have the estimated glomerular filtration rate (eGFR) determined prior to starting remdesivir and while receiving it. Safety data from patients with severe renal impairment and ESRD reported during study GS-US-540-5912 were 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 ESRD should be closely monitored for adverse events during treatment with remdesivir (see “Pharmacokinetics”).

Risk of reduced antiviral activity when co-administered with chloroquine or hydroxychloroquine

Co-administration of remdesivir and chloroquine phosphate or hydroxychloroquine sulphate is not recommended based on cell culture data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of remdesivir (see section “Interactions” and “Properties/Effects”).

Immunocompromised patients

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

Excipients

A 100 mg Veklury dose of powder for concentrate for solution for infusion contains approximately 211.8 mg sodium, equivalent to 10.6% of the WHO recommended maximum daily dietary intake of 2 g sodium for an adult.

Interactions

Pharmacodynamic interactions

Due to antagonism observed in cell culture, concomitant use of remdesivir with chloroquine phosphate or hydroxychloroquine sulphate is not recommended.

Pharmacokinetic interactions

Effect of Veklury on other medicinal products

Inhibition of enzymes

In vitro, remdesivir is an inhibitor of CYP3A4. At physiologically relevant concentrations, remdesivir or its metabolites GS-441524 and GS-704277 did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6 *in vitro*. *In vitro*, remdesivir is not a time-dependent inhibitor of CYP450 enzymes.
In vitro data indicate no clinically relevant inhibition of UGT1A3, 1A4, 1A6, 1A9 or 2B7 by remdesivir or its metabolites GS-441524 and GS-704277. Remdesivir, but not its metabolites, inhibited UGT1A1 *in vitro.*
Based on results from an *in vivo* drug interaction study with remdesivir and midazolam, remdesivir is not a clinically relevant inhibitor of CYP3A4. No clinically significant drug interactions are expected with remdesivir and UGT1A1 substrates.

Induction of enzymes

In vitro, remdesivir induced CYP1A2 and potentially CYP3A4, but not CYP2B6. Based on results from an *in vivo* drug interaction study, remdesivir is not a clinically relevant inducer of CYP3A4. No clinically significant drug interaction is expected with remdesivir and CYP1A2 substrates.

Inhibition of transporters

In vitro, remdesivir inhibited OAT3, OCT1, MATE-1 Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and 1B3 (OATP1B3). No inhibition potential is predicted for OAT1, OCT2 and MATE2-K.

At physiologically relevant concentrations, remdesivir and its metabolites did not inhibit P-glycoprotein (P-gp) and BCRP *in vitro.*
Based on results from an *in vivo* drug interaction study with remdesivir and pitavastatin, remdesivir is not a clinically relevant inhibitor of OATP1B1 and OATP1B3. No clinically significant drug interactions are expected with remdesivir and substrates of OAT3, OCT1 and MATE-1.

Drug-drug interaction studies were conducted with remdesivir. Table 5 summarises the effect of remdesivir on the pharmacokinetics of studied drugs.

Table 5: Effect of Remdesivir on other drugs

Co-administered Drug Dose (mg)	Remdesivir Dose (mg)	Interaction Geometric mean ratio (90% CI)	Recommendations for co-administration
Midazolam 2.5 single dose	200 single dose	↑ C_{max} 1.29 (1.19-1.41)[a] ↑ AUC_{inf} 1.20 (1.14-1.26)[a] No inhibition is expected when co-administering remdesivir with substrate of CYP3A	No dose adjustment of remdesivir is required when it is co-administered with substrate of CYP3A
Midazolam 2.5 single dose	200 single dose followed by 100 once daily (10 doses)[b]	↑ C_{max} 1.45 (1.23-1.70)[c] ↑ AUC_{inf} 1.30 (1.16-1.45)[c] No induction is expected when co-administering remdesivir with substrate of CYP3A	
Pitavastatin 2 single dose	200 single dose	↑ C_{max} 1.05 (0.92-1.20)[a] ↑ AUC_{inf} 1.17 (1.09-1.24)[a] No inhibition is expected when co-administering remdesivir with substrate of OATP1B1/OATP1B3	No dose adjustment of remdesivir is required when it is co-administered with substrate of OATP1B1/OATP1B3

NOTE: Interaction study conducted in healthy volunteers.
CI: Confidence Interval.
a. No effect = 1.00 (0.80-1.25).

b. Midazolam administered with last dose of remdesivir.
c. No effect = 1.00 (0.70-1.43).

Based on clinical drug interaction studies with remdesivir, no clinically significant drug interactions are expected with substrates of CYP1A2, CYP3A4 (including dexamethasone), UGT1A1, MATE1, OAT3, OCT1, OATP1B1 and OATP1B3.

Effect of other medicinal products on Veklury

In vitro, remdesivir is a substrate for esterases in plasma and tissue, drug metabolising enzyme CYP3A4, and is a substrate for OATP1B1 and P-gp transporters. GS-704277 is a substrate for OATP1B1 and OATP1B3. For GS-441524 and GS-704277, the only enzyme for which metabolism could be detected was UGT1A3.

A drug-drug interaction study was conducted with remdesivir. Table 6 summarises the pharmacokinetic effects of studied drugs on remdesivir and metabolites GS-704277 and GS-441524.

Table 6: Effect of Other Drugs on Remdesivir and Metabolites GS-704277 and GS-441524

Co-administered Drug Dose (mg)	Interaction Geometric mean ratio (90% CI)			Recommendation for co-administration
Cyclosporin 400 single dose	remdesivir	↑ C_{max}	1.49 (1.38-1.60)	No dose adjustment of remdesivir is required when it is co-administered with inhibitors of OATP1B1 and OATP1B3.
		↑ AUC_{inf}	1.89 (1.77-2.02)	
	GS-704277	↑ C_{max}	2.51 (2.26-2.78)	
		↑ AUC_{inf}	2.97 (2.75-3.20)	
	GS-441524	↑ C_{max}	1.17 (1.12-1.22)	
		↔ AUC_{inf}	1.03 (0.99-1.08)	
	No interactions are expected when co-administering remdesivir with inhibitors of OATP1B1/1B3 and/or P-gp.			
Carbamazepine 300 twice daily	remdesivir	↓ C_{max}	0.87 (0.78-0.97)	No dose adjustment of remdesivir is required when it is co-administered with strong CYP3A4 ~~and/or P-~~gp inducers.
		↓ AUC_{inf}	0.92 (0.83-1.02)	
	GS-704277	↔ C_{max}	0.96 (0.84-1.10)	
		↔ AUC_{inf}	0.98 (0.92-1.05)	
	GS-441524	↔ C_{max}	0.97 (0.88-1.07)	
		↓ AUC_{inf}	0.83 (0.78-0.89)	
	No interactions are expected when co-administering remdesivir with strong CYP3A4 inducers or CYP3A4 inhibitors.			

NOTE: Interaction study conducted in healthy participants with single 100 mg doses of remdesivir.
CI: Confidence Interval.

Pregnancy, lactation

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

Pregnancy

So far there is very limited amount of data from the use of remdesivir in pregnant women (less than 300 pregnancy outcomes). Most of the exposures occured in the second, third or an unknown

trimester and available data do not indicate any risk. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see “Preclinical Data”). Due to very limited experience, remdesivir should not be used during first trimester in pregnancy unless the clinical condition of the woman requires treatment with it. Use in the second and third trimester of pregnancy may be considered.

Lactation

Remdesivir and its major metabolite are excreted 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. As the clinical experience is limited, a decision about breast-feeding during treatment should be made after a careful individual benefit-risk assessment.

Fertility

No human data on the effect of remdesivir on fertility are available. In male rats, there was no effect on mating or fertility with remdesivir treatment. In female rats, however, an impairment of fertility was observed (see “Preclinical data”). The relevance for humans is unknown.

Effects on ability to drive and use machines

No corresponding studies have been performed.

Undesirable effects

Summary of the safety profile

The safety profile of Veklury is based on data from 4 Phase 1 studies in healthy adults, 3 Phase 3 studies in hospitalised patients with COVID-19, 1 Phase 3 study in non-hospitalised patients with COVID-19, from hospitalised patients with COVID-19 who received Veklury in a compassionate use program and from post-marketing experience. The most common adverse reaction in healthy participants is increased transaminases (14%). The most common adverse reaction in patients with COVID-19 is nausea (4%).

Tabulated summary of adverse reactions

The adverse reactions in Table 7 are listed below by system organ class and frequency. Frequencies are defined as follows: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), not known (frequency cannot be estimated from the available data).

Table 7: Tabulated list of adverse reactions

Frequency	Adverse reaction
Immune system disorders	
Rare	hypersensitivity
Not known	anaphylactic reaction[a], anaphylactic shock[a]
Nervous system disorders	
Common	headache
Cardiac disorders	
Not known	sinus bradycardia[b]
Gastrointestinal disorders	
Common	nausea
Hepatobiliary disorders	
Very common	transaminases increased (14%)
Skin and subcutaneous tissue disorders	
Common	rash
Investigations	
Very common	prothrombin time prolonged (44%)
Injury, poisoning and procedural complications	
Rare	infusion-related reaction

[a] Adverse reaction identified through post-marketing surveillance.
[b] Reported in post-marketing, usually normalised within 4 days following last Veklury administration without additional intervention.

Description of selected undesirable effects

Transaminases increased

In healthy participant studies, increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST) or both in participants who received remdesivir were grade 1 (10%) or grade 2 (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 increased

In a clinical study (NIAID ACTT-1) of patients with COVID-19, the incidence of increased prothrombin time or INR (predominantly Grades 1-2) was higher in participants who received remdesivir compared to placebo, with no difference observed 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 impaired renal function

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 “Warnings and precautions” and “Properties/effects”). 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 observed in the incidence of bleeding events between the two groups.

Pregnancy

In study CO-US-540-5961 (IMPAACT 2032), 25 hospitalised pregnant and 28 nonpregnant women of childbearing potential received remdesivir 200 mg on Day 1 followed by remdesivir 100 mg once daily for up to 9 days (for a total of up to 10 days, as appropriate) (see “Pharmacokinetics”).
There were no new safety findings from infusion to 4 weeks post last infusion when remdesivir was administered to pregnant and non-pregnant women hospitalised with COVID-19, or 24 hours post-delivery, compared with the known safety profile of remdesivir in COVID-19 infected adults. There were no adverse reactions in infants born during the study (n=16).

Paediatric population

The safety assessment of remdesivir in children with COVID-19 is based on data from a Phase 2/3, open-label clinical study (Study GS-US-540-5823) that enrolled 58 patients who were treated with remdesivir. The adverse reactions observed were consistent with those observed in clinical trials of remdesivir in adults. Additionally, isolated cases of upper abdominal pain, constipation, hemoglobin decreased, and hyperbilirubinaemia were observed as adverse reactions in GS-US-540-5823.

Reporting of suspected undesirable effects

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

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

Properties/Effects

ATC code

J05AB16

Mechanism of action

Remdesivir is an adenosine nucleotide prodrug that is metabolized within host cells to form the pharmacologically active nucleoside triphosphate metabolite. Remdesivir triphosphate acts as an analog of adenosine triphosphate (ATP) and competes with the natural ATP substrate for incorporation into nascent RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase, which

results in delayed chain termination during replication of the viral RNA. As an additional mechanism, remdesivir triphosphate can also 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.

Pharmacodynamics

Antiviral Activity

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.

The antiviral activity of remdesivir was antagonised by chloroquine phosphate in a dose-dependent manner when the two drugs were co-incubated at clinically relevant concentrations in HEp-2 cells infected with respiratory syncytial virus (RSV). Higher remdesivir EC_{50} values were observed with increasing concentrations of chloroquine phosphate. Increasing concentrations of chloroquine phosphate reduced formation of remdesivir triphosphate in A 549-hACE2, HEp-2 and normal human bronchial epithelial cells.

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.2.86, 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, EG.5.1.4, FL.22, HK.3, HV.1, JN.1, XBB, XBB.1.5, XBB.1.5.72, XBB.1.16, XBB.2.3.2, XBC.1.6 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 JN.1.7, JN.1.18, KP.2, KP.3, LB.1 and XBB.1.9.2 compared to the wildtype reference replicon (lineage B).

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 (see “Clinical Efficacy”), 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 (see “Clinical efficacy”), among 19 patients treated with remdesivir who had baseline and post-baseline sequencing data available, substitutions in the viral RNA-dependent RNA polymerase (nsp12) were observed in 4 patients. The substitutions observed were not associated with resistance to remdesivir (≤ 1.45-fold) (T76I, A526V, A554V, C697F) or could not be determined due to lack of replication (E665K).

In GS-US-540-9012 Study (see “Clinical efficacy”), 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). This patient was not hospitalised and showed alleviation of all baseline symptoms, except loss of taste and smell, prior to or on Day 14. 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 (see “Pharmacokinetics”), 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 (see “Clinical efficacy”), among patients with baseline and post-baseline sequencing data available, substitutions in the viral RNA-dependent RNA polymerase (nsp12) were observed in 3 of 28 patients treated with remdesivir. The substitutions observed have not been associated with resistance to remdesivir (≤ 1.85-fold change in EC_{50} relative to reference) (V166L, G670V) or their impact on susceptibility to remdesivir could not be determined due to lack of replication in a subgenomic replicon assay (V495F, A656P, A656P+G670V). No substitutions observed in other proteins of the replication-transcription complex were associated with resistance to remdesivir.

QT

In a thorough QT/QTc trial that dosed 60 healthy subjects with 600 mg of remdesivir as a single treatment, no effect was seen on the QTc interval.

Clinical efficacy

Clinical Studies in Patients with COVID-19

NIAID ACTT-1 Study (CO-US-540-5776)

A randomised, double-blind, placebo-controlled clinical study evaluated 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) in hospitalised adult patients with COVID-19 with evidence of lower respiratory tract involvement. The study enrolled 1062 hospitalised patients: 105 (9.9%) patients

with mild/moderate disease (10% in both treatment groups) and 957 (90.1%) patients with severe disease (90% 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 an SpO2 ≤ 94% on room air, a respiratory rate ≥ 24 breaths/min, 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%), 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).
The outcome differed relevantly between the two strata. In the severe disease stratum time to recovery was 11 days in the remdesivir group and 18 days in the placebo group (recovery rate ratio 1.31 [95% CI 1.12 to 1.52]). For the mild/moderate disease stratum, time to recovery was not different between the two groups (5 days for both, remdesivir and placebo).

The clinical benefit of remdesivir was most apparent in patients receiving oxygen, however, not on high-flow oxygen or ventilation, at Day 1 (recovery rate ratio 1.45 [95% CI 1.18 to 1.79]). For patients who were receiving mechanical ventilation or ECMO on Day 1, no difference in recovery rate was observed between the treatment groups (0.98 [95% CI 0.70 to 1.36]).

Overall, 29-day mortality 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).

Study GS-US-540-5773 in patients with severe COVID-19

A randomised, open-label multi-centre clinical study (GS-US-540-5773) of patients at least 12 years of age with confirmed SARS-CoV-2 infection, oxygen saturation ≤ 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. Patients on mechanical ventilation at screening were excluded. 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.

At baseline, the median age of patients was 61 years (range, 20 to 98 years); 64% were male, 75% were White, 12% were Black, and 12% were Asian. More patients in the 10-day group than the 5-day group required invasive mechanical ventilation or ECMO (5% vs 2%), or high-flow oxygen support (30% vs 25%), at baseline. Median duration of symptoms and hospitalisation prior to first dose of remdesivir were similar across treatment groups.

Overall, after adjusting for between-group differences at baseline, patients receiving a 5-day course of remdesivir had similar clinical status at Day 14 as those receiving a 10-day course (odds ratio for improvement: 0.75; [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.

Study GS-US-540-5774 in patients with moderate COVID-19

A randomised, open-label multi-centre clinical study (GS-US-540-5774) of hospitalised patients at least 12 years of age with confirmed SARS-CoV-2 infection and radiological evidence of pneumonia without reduced oxygen levels compared treatment with remdesivir for 5 days (n=191) and treatment with remdesivir for 10 days (n=193) with standard of care (n=200). Patients treated with remdesivir received 200 mg on Day 1 and 100 mg once daily on subsequent days. The primary endpoint was clinical status on Day 11 assessed on a 7-point ordinal scale ranging from hospital discharge to increasing levels of oxygen and ventilatory support to death.

At baseline, the median age of patients was 57 years (range, 12 to 95 years); 61% were male, 61% were White, 19% were Black, and 19% were Asian. Baseline clinical status, oxygen support status, and median duration of symptoms and hospitalisation prior to first dose of remdesivir were similar across treatment groups.

Overall, the odds of improvement in the ordinal scale were higher in the 5-day remdesivir group at Day 11 when compared to those receiving only standard of care (odds ratio, 1.65; [95% CI, 1.09 to 2.48], p=0.017). The odds of improvement in clinical status with the 10-day treatment group when compared to those receiving only standard of care were not statistically significant (odds ratio 1.31; [95% CI 0.88 to 1.95]). All-cause 28-day mortality for the 5-day, 10-day, and standard of care groups was 1%, 1.6%, and 2%, respectively.

Study GS-US-540-9012 in patients with confirmed COVID-19 at high risk for disease progression

A randomised, double-blind, placebo-controlled, clinical trial (GS-US-540-9012) evaluated remdesivir 200 mg once daily for 1 day followed by remdesivir 100 mg once daily for 2 days (for a total of 3 days of intravenously administered therapy) in 562 patients, including 8 adolescents (12 years of age and older and weighing at least 40 kg) with confirmed SARS-CoV-2 infection and at least one risk factor for progression to hospitalisation. Risk factors for disease progression were: aged ≥ 60 years, chronic lung disease, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity, immunocompromised state, chronic mild or moderate kidney disease, chronic liver disease, current cancer, or sickle cell disease. Vaccinated patients were excluded from the study.

Patients were randomised 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, 80% were White, 8% were Black, 2% were Asian, 44% were Hispanic or Latino; 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 well balanced across the remdesivir and placebo treatment groups. Post-hoc exploratory analysis of optional biomarker samples showed 14.8% of patients were serological positive at baseline and 37.7% were serological negative (47.5% did not consent to optional biomarker collection).

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. Events (COVID-19-related hospitalisation or all-cause 28-day mortality) occurred in 2 (0.7%) patients treated with remdesivir compared to 15 (5.3%) patients concurrently randomised to placebo, demonstrating 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). No deaths were observed at Day 28. Six of the 17 hospitalisation events occurred in participants with known baseline serostatus (serological positive: n=0 in remdesivir group and n=2 in placebo group; serological negative: n=2 in remdesivir group and n=2 in placebo group). Eleven of the 17 hospitalisation events occurred in participants with unknown baseline serostatus in placebo group and none in the remdesivir group. No conclusion can be made on efficacy in the subgroups stratified by serostatus due to the small number of patients with known serostatus and overall low event rates.

Paediatric population

Study GS-US-540-5823 is a single-arm, open-label study where the pharmacokinetics and safety of remdesivir in paediatric patients with COVID-19 (n=58) was assessed. Efficacy endpoints based on the clinical status (assessed on a 7-point ordinal scale ranging from death [score of 1] to ventilatory support and decreasing levels of oxygen to hospital discharge [score of 7]) were secondary and only descriptively analysed and therefore these should be interpreted with caution.

Infants, children and adolescents (Cohorts 1-4 and 8) *(n=53)*:

Patients weighing ≥ 40 kg received 200 mg of remdesivir on Day 1 followed by remdesivir 100 mg once daily on subsequent days; 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. A total of 13 patients (24.5%) received remdesivir for 10 days.

At baseline, median age was 7 years (range: 0.1 to 17 years); 57% were female, 70% were White, 30% were Black, and 44% were Hispanic or Latino; 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); 7 (58%), 2 (17%), 3 (27%), 3 (27%), and 4 (80%) patients in Cohorts 1, 2, 3, 4 and 8 respectively. The most common comorbidities were asthma (28%) and cardiac disorders (21%). A total of 12 patients (23%) were on invasive mechanical ventilation, 18 (34%) were on non-invasive ventilation or high-flow oxygen; 10 (19%) were on low-flow oxygen; and 13 (25%) were on room air, 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 Cohorts 1-4 and 8, the median (Q1, Q3) change from baseline in clinical status was +2.0 (1.0, 4.0) points on Day 10. Recovery (defined as an improvement from a baseline clinical status score of 2 through 5 to a score of 6 or 7, or an improvement from a baseline score of 6 to a score of 7) was reported for 62% of patients on Day 10; 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 modulators and anti-inflammatory agents. Three patients died in these cohorts in the study.

Neonates, and preterm neonates and infants (Cohorts 5-7) (n=5):

Full-term neonates 14 days to less than 28 days old and weighing at least 2.5 kg received remdesivir 5 mg/kg on Day 1 followed by remdesivir 2.5 mg/kg once daily on subsequent days; full-term neonates less than 14 days old and weighing at least 2.5 kg at birth and preterm neonates and infants less than 56 days old and weighing at least 1.5 kg at birth received remdesivir 2.5 mg/kg on Day 1 followed by remdesivir 1.25 mg/kg once daily on subsequent days.

At baseline, patients ranged in age from 12 to 30 days; 3/5 were female, 4/5 were White; weight ranged from 2.2 to 3.5 kg. Three patients were on invasive mechanical ventilation and 2 were on high-flow oxygen. The duration of symptoms and hospitalisation prior to first dose of remdesivir ranged from 2 to 9 days and 1 to 9 days, respectively.

In Cohorts 5-7 recovery was reported for one patient by Day 10. Time to recovery for patients who had recovered by the time of the last assessment (n=3) ranged from 9 to 19 days. One patient was discharged by Day 10. However, given the limited sample size, safety and efficacy were not established in these patients. No patients died in these cohorts the study.

Pharmacokinetics

The pharmacokinetic properties of remdesivir have been investigated in healthy participants and patients with COVID-19.

Absorption

The pharmacokinetic properties of remdesivir and the predominant circulating metabolite GS-441524 have been evaluated in healthy adult participants. Following intravenous administration of remdesivir adult dosage regimen, peak plasma concentration was observed at end of infusion, regardless of dose level, and declined rapidly thereafter with a half-life of approximately 1 hour. Peak plasma concentrations of GS-441524 were observed at 1.5 to 2.0 hours post start of a 30 minute infusion.

Distribution

Remdesivir is approximately 88 to 93% bound to human plasma proteins (*ex-vivo* data). The binding is independent of drug concentration over the range of 1 to 10 µM, with no evidence for saturation of remdesivir binding. Protein binding of GS-441524 was low (2% bound) in human plasma. After a single 150 mg dose of [^{14}C]-remdesivir in healthy participants, the blood to plasma ratio of ^{14}C-radioactivity was approximately 0.68 at 15 minutes from start of infusion, increased over time reaching ratio of 1.0 at 5 hours, indicating differential distribution of remdesivir and its metabolites to plasma or cellular components of blood.

Metabolism

Remdesivir is extensively metabolized to the pharmacologically active nucleoside analog triphosphate GS-443902 (formed intracellularly). The metabolic activation pathway involves initial hydrolysis to an intermediate metabolite, GS-704277. This reaction is catalyzed primarily (80%) by CES1 enzymes, with minor contributions from cathepsin A and CYP3A (approximately 10% each). Phosphoramidate cleavage of GS-704277, catalyzed by the enzyme HINT1, is then followed by successive phosphorylation to form 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. The levels of thiocyanate detected

following administration of 100 mg and 200 mg remdesivir were observed to be significantly below endogenous levels in human plasma.

Elimination

Following a single 150 mg intravenous dose of [^{14}C]-remdesivir, mean total recovery of the dose was 92%, consisting of approximately 74% and 18% recovered in urine and feces, respectively. The majority of the remdesivir dose recovered in urine was GS-441524 (49%), while 10% was recovered as remdesivir. These data indicate that renal clearance is the major elimination pathway for GS-441524. The median terminal half-lives of remdesivir and GS-441524 were approximately 1 and 27 hours, respectively.

Pharmacokinetics of remdesivir and metabolites in adults with COVID-19

Pharmacokinetic exposures for remdesivir and its metabolites in adults with COVID-19 are provided in Table 8.

Table 8: Multiple Dose PK Parameters[a] of Remdesivir and Metabolites (GS-441524 and GS-704277) following IV Administration of Remdesivir 100 mg to Adults with COVID-19

Parameter Mean[b] (95%CI)	**Remdesivir**	**GS-441524**	**GS-704277**
C_{max} (ng/ml)	1650 (1570, 1730)	85.0 (78.8, 91.7)	128 (118, 139)
AUC_{tau} (ng•h/ml)	983 (946, 1020)	1410 (1290, 1530)	229 (219, 241)
C_{trough} (ng/ml)	ND	38.8 (35.7, 42.2)	ND

CI = Confidence Interval
ND = Not detectable (at 24 hours post-dose)
a. Population PK estimates for 30-minute IV infusion of remdesivir for 3 days (Study GS-US-540-9012, n=148).
b. Geometric mean estimates

Kinetics in specific patient groups

Age, gender and ethnicity

Based on age, gender or ethnicity pharmacokinetic differences on the exposures of remdesivir were evaluated using population pharmacokinetic analysis. Gender and ethnicity 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 years of age, however no dose adjustment is needed in these patients.

Hepatic impairment

The pharmacokinetics of remdesivir and its metabolites (GS-441524 and GS-704277) were evaluated in healthy participants 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 patients with normal hepatic function, mean exposures (AUC_{inf}, C_{max}) of remdesivir and GS-704277 were comparable in moderate hepatic

impairment and were up to 2.4 fold higher in severe hepatic impairment; however, the increase was not considered clinically significant.

Renal impairment

The pharmacokinetics of remdesivir and its metabolies (GS-441524 and GS-704277) and the excipient betadex sulfobutyl ether sodium (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 kidney failure (eGFR <15 ml/minute) on dialysis or not on dialysis following a single dose of up to 100 mg of remdesivir (Table 9); and in a Phase 3 study in COVID-19 patients with severely reduced kidney function (eGFR <30 ml/minute) receiving remdesivir 200 mg loading dose on Day 1 followed by 100 mg from Day 2 to Day 5 (Table 10). 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 20-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.

Table 9: Statistical comparison of pharmacokinetic parameters[a] of remdesivir and metabolites (GS-441524 and GS-704277) between adult subjects with decreased renal function[b] (mild, moderate, severe renal impairment and ESRD) and adult subjects with normal renal function

GLSM Ratio (90%CI)[c]	60-89 ml per minute n=10	30-59 ml per minute n=10	15-29 ml per minute n=10	< 15 ml per minute		
				Pre-hemodialysis n=6	Post-hemodialysis n=6	No dialysis n=3
Remdesivir						
AUC_{inf} (h•ng/ml)	99.5 (75.3, 132)	122 (97.5, 152)	94.2 (83.0, 107)	79.6 (59.0, 108)	108 (71.5, 163)	88.9 (55.2, 143)
C_{max} (ng/ml)	96.0 (70.5, 131)	120 (101, 142)	97.1 (83.3, 113)	89.1 (67.1, 118)	113 (79.4, 160)	93.9 (65.4, 135)
GS-441524						
AUC_{inf}[d] (h•ng/ml)	119 (96.7, 147)	202 (157, 262)	326 (239, 446)	497 (365, 677)	622 (444, 871)	787 (649, 953)
C_{max} (ng/ml)	107 (90.1, 126)	144 (113, 185)	168 (128, 220)	227 (172, 299)	307 (221, 426)	300 (263, 342)
GS-704277						
AUC_{inf} (h•ng/ml)	139 (113, 171)	201 (148, 273)	178 (127, 249)	218 (161, 295)	206 (142, 297)	281 (179, 443)
C_{max} (ng/ml)	225 (120, 420)	183 (134, 249)	127 (96.1, 168)	143 (100, 205)	123 (83.6, 180)	176 (119, 261)

CI=Confidence Interval; GLSM = geometric least-squares mean

a. Exposures were estimated using noncompartmental analysis from a dedicated Phase 1 renal impairment study GS-US-540-9015; single doses up to 100 mg were administered; each subject with renal impairment had a matched control

participant enrolled with normal renal function (eGFR ≥90 ml/min/1.73m^2), same sex, and similar BMI (± 20%) and age (± 10 years).
b. eGFR was calculated using Modification of Diet in Renal Disease equation and reported in ml/min/1.73 m^2.
c. Ratio calculated for the comparison of PK parameters of test (subjects with reduced renal function) to reference (subjects with normal renal function).
d. $AUC_{0\text{-}72h}$ for subjects on haemodialysis.

Table 10: Pharmacokinetic parameters[a] of remdesivir and metabolites (GS-441524 and GS-704277) following IV administration of remdesivir (200 mg on Day 1 followed by 100 mg daily on Days 2-5) to adults with COVID-19 and severely reduced kidney function (eGFR <30 ml/min)

Parameter Mean[b] (percentile, 5th, 95th)	Remdesivir	GS-441524	GS-704277
AUC_{tau} (h•ng/ml)	1700 (1030, 2970)	7580 (1630, 18600)	919 (509, 1620)
C_{max} (ng/ml)	2090 (890, 4360)	349 (72.4, 818)	232 (61.9, 613)

a. Population PK estimates for 30-minute IV infusion of remdesivir for 5 days (study GS-US-540-5912, n=90).
b. Geometric mean estimates.

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 nonpregnant women of child-bearing potential.

Paediatric patients

Population pharmacokinetic models for remdesivir and its circulating metabolites (GS-704277 and GS-441524), developed using pooled data from studies in healthy adults 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) (Table 11). Geometric mean exposures ($AUC_{tau,}$ C_{max} and C_{tau}) for patients > 28 days to < 18 years old and weighing > 3 kg (Cohorts 1-4 and 8, n=50) at the doses administered were 1% to 40% higher for remdesivir, 26% lower to 4% higher for GS-441524 and 13% lower to 95% higher for GS-704277 as compared to those in adult patients with COVID-19. The differences were not considered clinically relevant. Plasma exposures of excipient SBECD were generally similar for all paediatric patients at the doses administered in GS-US-540-5823 study and were similar compared to adults with normal renal function, although data are very limited.

Table 11: Pharmacokinetic parameters[a] estimate of steady-state plasma remdesivir, GS-441524 and GS-704277 in paediatric and adult hospitalised COVID-19 patients

Parameters Mean[b]	Paediatric patients					Adult hospitalised patients (N=289)
	Cohort 1	Cohort 8	Cohort 2	Cohort 3	Cohort 4	
	12 to <18 years and weighing ≥40 kg (N=12)	<12 years and weighing ≥40 kg (N=5)	28 days to <18 years and weighing 20 to <40 kg (N=12)	28 days to <18 years and weighing 12 to <20 kg (N=11)	28 days to <18 years and weighing 3 to <12 kg (N=10)	
Remdesivir						
AUC_{tau} (h•ng/ml)	1450	1430	1990	1940	1500	1420
C_{max} (ng/ml)	2220	2440	2990	2570	2460	2160
GS-441524						
AUC_{tau} (h•ng/ml)	1480	1460	1520	1530	1660	1930
C_{max} (ng/ml)	85.3	96.5	106	105	120	116
C_{tau} (ng/ml)	44.1	42.3	44.5	44.3	47.8	55.3
GS-704277						
AUC_{tau} (h•ng/ml)	390	351	574	390	390	400
C_{max} (ng/ml)	163	219	367	223	267	188

a. PK parameters were simulated using PopPK modeling with 0.5 hour of duration for remdesivir infusions.
b. Geometric mean estimates.
Paediatric hospitalised patients are from Study GS-US-540-5823; patients received 200 mg on Day 1 followed by remdesivir 100 mg once daily on subsequent days (Cohort 1 and 8), or 5 mg/kg on Day 1 followed by remdesivir 2.5 mg/kg once daily on subsequent days (Cohort 2-4) for a total treatment duration of up to 10 days.
Adult hospitalised patients are from Study CO-US-540-5844 (a phase 3 randomised study to evaluate the safety and antiviral activity of remdesivir in patients with severe COVID-19); patients received 200 mg on
Day 1 followed by remdesivir 100 mg once daily on subsequent days (10 days total treatment duration).

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.

Preclinical 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 at dosage levels of 5, 10, and 20 mg/kg/day for 7 days resulted, at all dose levels, in increased mean urea nitrogen and increased mean creatinine, renal tubular atrophy, and basophilia and casts, and an unscheduled death of one animal at the 20 mg/kg/day dose level. In rats at dosage levels of > 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 (rat at 3 mg/kg/day) the exposure in humans following intravenous administration at the recommended human dose (RHD).

Genotoxicity

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.

Carcinogenicity

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

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 embryofoetal 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 animal studies, the nucleoside analog metabolite GS-441524 has been detected in the blood of nursing rat pups of mothers given remdesivir. Therefore, excretion of remdesivir and/or metabolites into the milk of lactating animals can be assumed.

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.

Other information

Incompatibilities

This medicinal product must not be mixed or administered with simultaneously other medicinal products in the same dedicated line except those mentioned in section “Instructions for handling”.

Shelf life

Do not use this medicinal product after the expiry date (“EXP”) stated on the container.

Shelf life after opening

Reconstituted and diluted solution for infusion
Store diluted Veklury solution for infusion up to 24 hours at below 25°C or 48 hours in a refrigerator (2°C to 8°C).

Special precautions for storage

Keep out of reach of children.
Do not store above 30°C.
For storage conditions after reconstitution and dilution of the medicinal product, see “Shelf life after opening”.

Instructions for handling

Prepare solution for infusion under aseptic conditions and on the same day as administration. Veklury should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Should either be observed, the solution should be discarded and fresh solution prepared.

Veklury must be reconstituted with 19 ml sterile water for injections and diluted in sodium chloride 9 mg/ml (0.9%) solution for injection before being administered via intravenous infusion over 30 to 120 minutes.

Preparation of Veklury solution for infusion

Reconstitution

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

- Aseptically 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, and insert the needle in the centre of the vial stopper.
  - Discard the vial if a vacuum does not pull the sterile water for injections into the vial.
- Only use **sterile water** for injection to reconstitute Veklury.
- Immediately shake the vial for 30 seconds.
- Allow the contents of the vial to settle for 2 to 3 minutes. A clear solution should result.
- If the contents of the vial are not completely dissolved, shake the vial again for 30 seconds and allow the contents to settle for 2 to 3 minutes. Repeat this procedure as necessary until the contents of the vial are completely dissolved.
- Inspect the vial to ensure the container closure is free from defects and the solution is free of particulate matter.
- Dilute immediately after reconstitution.

Dilution

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

Adults and paediatric patients (weighing at least 40 kg)

- Using Table 12, determine the volume of sodium chloride 9 mg/ml (0.9%) solution for injection to withdraw from the infusion bag.

Table 12: Recommended dilution instructions - Reconstituted Veklury powder for concentrate for solution for infusion

Veklury dose	Sodium chloride 9 mg/ml (0.9%) infusion bag volume to be used	Volume to be withdrawn and discarded from sodium chloride 9 mg/ml (0.9%) infusion bag	Required volume of reconstituted Veklury
200 mg (2 vials)	250 ml	40 ml	2 x 20 ml
	100 ml	40 ml	2 x 20 ml
100 mg (1 vial)	250 ml	20 ml	20 ml
	100 ml	20 ml	20 ml

NOTE: 100 ml should be reserved for patients with severe fluid restriction, e.g. with ARDS or renal failure.

- Withdraw and discard the required volume of sodium chloride 9 mg/ml from the bag using an appropriately sized syringe and needle per Table 12.
- Withdraw the required volume of reconstituted remdesivir powder for concentrate for solution for infusion using an appropriately sized syringe per Table 12. Discard any unused portion remaining in the remdesivir vial.
- Transfer the required volume of reconstituted remdesivir powder for concentrate for solution for infusion to the selected infusion bag.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- The prepared solution is stable for 24 hours at room temperature (20°C to 25°C) or 48 hours in the refrigerator (at 2°C to 8°C) (including any time before dilution into intravenous infusion fluids).

Paediatric patients (at least 4 weeks of age weighing at least 3 kg to less than 40 kg)

- Further dilute the 100 mg/20 ml (5 mg/ml) remdesivir concentrate to a fixed concentration of 1.25 mg/ml using sodium chloride 9 mg/ml.
- The total required infusion volume of the 1.25 mg/ml remdesivir solution for infusion is calculated from the paediatric weight-based dosing regimens of 5 mg/kg for the Loading Dose and 2.5 mg/kg for each Maintenance Dose.
- Small sodium chloride 9 mg/ml infusion bags (e.g., 25, 50, or 100 ml) or an appropriately sized syringe should be used for paediatric dosing. The recommended dose is administered via IV infusion in a total volume dependent on the dose to yield the target remdesivir concentration of 1.25 mg/ml.
- A syringe may be used for delivering volumes <50 ml.

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

Disposal

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

Authorisation number

68026 (Swissmedic)

Packs

Veklury 100 mg powder for concentrate for solution for infusion: 1 vial [A]

Marketing authorisation holder

Gilead Sciences Switzerland Sàrl, Zug

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