Date: 22 January 2021
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Veklury

International non-proprietary name: remdesivir

Pharmaceutical form: powder for concentrate for solution for infusion and concentrate for solution for infusion

Dosage strength: 100 mg

Route(s) of administration: intravenous use

Marketing Authorisation Holder: Gilead Sciences Switzerland Sàrl

Marketing Authorisation No.: 68026 and 68043

Decision and Decision date: approved (temporary authorisation in accordance with Art. 9a TPA) on 25 November 2020

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
BCRP	Breast cancer resistance protein
BSEP	Bile Salt Export Pump
Cmax	Maximum observed plasma/serum concentration of drug
CoV	Coronavirus
COVID-19	Coronavirus disease 2019
CSR	Clinical study report
CYP	Cytochrome P450
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
EC_{50}	Half maximal effective concentration
ECMO	Extracorporeal membrane oxygenation
eGFR	Estimated glomerular filtration rate
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
IC_{50}	Half-maximal inhibitory concentration
ICH	International Council for Harmonisation
ICU	Intensive Care Unit
Ig	Immunoglobulin
INN	International Nonproprietary Name
IQR	Interquartile range
IV	Intravenous
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MERS	Middle East respiratory syndrome
Min	Minimum
MRP	Multidrug resistance-associated protein
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
NTCP	Sodium taurocholate cotransporting polypeptide
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PBMCs	Peripheral blood mononuclear cells
PD	Pharmacodynamics
P-gp	P-glycoprotein
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RDV	Remdesivir
RNA	Ribonucleic acid

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RMP	Risk Management Plan
SARS-COV-2	Severe acute respiratory syndrome coronavirus-2
SOC	Standard of care
SpO2	Oxygen saturation
SwissPAR	Swiss Public Assessment Report
$T_{1/2}$	Half-life
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
UGT	Uridine 5'-Diphospho-Glucuronosyltransferase
WHO	World Health Organisation

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance remdesivir of the medicinal product mentioned above.

Temporary authorisation for human medical products
The applicant requested a temporary authorisation in accordance with Art. 9a TPA.

2.2 Indication and Dosage

2.2.1 Requested Indication

Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen (see "Properties/Effects").

2.2.2 Approved Indication (temporary authorisation in accordance with Art. 9a TPA.)

Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults with pneumonia requiring supplemental oxygen (see "Properties/Effects").

2.2.3 Requested Dosage

Use of Veklury is confined to healthcare facilities in which patients can be monitored closely (see section "Warnings and precautions").

The recommended dosage of Veklury in patients 12 years of age and older and weighing at least 40 kg is:

- Day 1 – single loading dose of remdesivir 200 mg given by intravenous infusion
- Day 2 onwards – remdesivir 100 mg given once daily by intravenous infusion.

Duration of treatment
The total duration of treatment should be at least 5 days and not more than 10 days.

Special dosage instructions

Patients with impaired hepatic function

The pharmacokinetics of Veklury have not been evaluated in patients with hepatic impairment. It is not known if dosage adjustment is appropriate in patients with hepatic impairment (see "Warnings and precautions" and "Pharmacokinetics").

Patients with impaired renal function

The pharmacokinetics of Veklury have not been evaluated in patients with renal impairment. Patients with eGFR ≥ 30 ml/min have received remdesivir for treatment of COVID-19 with no dose adjustment. Veklury should not be used in patients with eGFR < 30 ml/min (see "Warnings and precautions" and "Pharmacokinetics").

Elderly patients

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

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Paediatric patients

The safety and efficacy of Veklury in children under the age of 12 years and weighing < 40 kg have not yet been established. No data are available.

Mode of administration

Veklury 100 mg powder for concentrate for solution for infusion

For intravenous use.

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

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

Veklury 100 mg concentrate for solution for infusion
For intravenous use.

Veklury is for administration by intravenous infusion after further dilution.

It must not be given as an IM injection.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Für die Arzneimittel Veklury, Pulver für ein Konzentrat zur Herstellung einer Infusionslösung und Veklury, Konzentrat zur Herstellung einer Infusionslösung hat die Swissmedic am 30 Juni 2020 mit Verfügung festgestellt, dass sie auf der Grundlage von Art. 21 Abs. 1 der Verordnung 3 über Massnahmen zur Bekämpfung des Coronavirus (COVID-19; COVID-19-Verordnung 3 [SR 818.101.24]) ab dem Zeitpunkt des Einreichens eines vollständigen Zulassungsgesuchs bis zum Zulassungsentscheid der Swissmedic oder bis zur Aufhebung der entsprechenden notrechtlichen Grundlage ohne Zulassung in der Schweiz in Verkehr gebracht werden dürfen.

Application	30 June 2020
Feststellungsverfügung	30 June 2020
Formal control completed	1 July 2020
Predecision	10 September 2020
Answers to Predecision	16 October 2020
Labelling corrections	19 October 2020
Answers to Labelling corrections:	9 November 2020
Final Decision	25 November 2020
Decision	Approval (temporary authorisation in accordance with Art. 9a TPA)

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3 Medical Context

Coronavirus Disease 2019 (COVID-19) is the disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Since it first emerged in Wuhan, China, in December 2019, the disease has rapidly spread globally. It was declared a pandemic by WHO in March 2020.

COVID-19 can range from mild to severe disease, with the majority (approximately 80%) of patients having mild to moderate disease, including flu-like symptoms up to mild pneumonia. A part of those who are infected remain asymptomatic, but the exact proportion of asymptomatic infections is currently unknown. Most symptomatic patients develop symptoms within 11.5 days, with an estimated median incubation time of 4-5 days.[1]

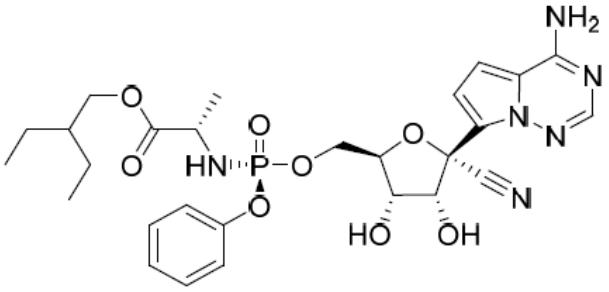
About 20% of infected patients develop severe to critical disease with complications including acute respiratory distress syndrome (ARDS), arrhythmia, septic shock, acute cardiac injury, acute coronary syndrome, cardiomyopathy, acute respiratory injury, and acute renal injury, likely as a result of a hyperinflammatory response.[1, 2, 3] Important risk factors for a severe course of disease are older age and/or specific medical conditions such as cancer, chronic kidney disease, chronic obstructive pulmonary disease (COPD), immunocompromised state, obesity, serious heart conditions, sickle cell disease or diabetes mellitus type 2.[1]

At the time of submission, there were no approved drugs to treat COVID-19 in Switzerland.

4 Quality Aspects

4.1 Drug Substance

INN:	Remdesivir
Chemical name:	2-Ethylbutyl (2S)-2-{[(S)-{[(2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f] [1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl] methoxy}(phenoxy) phosphoryl] amino}propanoate
Molecular formula:	$C_{27}H_{35}N_6O_8P$
Molecular mass:	602.6
Molecular structure:	



Remdesivir is a white to off-white or yellow solid. Remdesivir is practically insoluble in water and is not hygroscopic. Remdesivir has six stereocentres and is produced as a single stereoisomer.
The drug substance is manufactured by a multiple-step chemical synthesis with final isolation by crystallisation.
The structure of remdesivir has been fully elucidated using several spectroscopic techniques.
The drug substance specification includes relevant tests for proper quality control, encompassing tests relating to identification, assay, impurities, residual solvents, endotoxins and water content.
Appropriate stability data have been presented and justify the established re-test period.

[1] CDC Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (updated 30 June 2020).

[2] Xie Y., Wang Z., Liao H., Marley G., Wu D., Tang, W. Epidemiologic, clinical, and laboratory findings of the COVID-19 in the current pandemic: systematic review and meta-analysis. BMC Infect Dis. 2020;20:640.

[3] Zhong J., Tang J., Ye C., Dong L. The immunology of COVID-19: is immune modulation an option for treatment? Lancet Rheumatol. 2020;2:e428–e436.

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4.2 Drug Product

Drug Product: Powder for concentrate for solution for infusion
The finished product (powder for concentrate for solution) is a preservative-free, white to off-white to yellow lyophilised solid containing 100 mg of remdesivir.
The powder form contains 100 mg of remdesivir that is to be reconstituted with 19 mL of sterile water for injection and diluted in intravenous infusion fluids prior to intravenous administration. Following reconstitution, each vial contains a 5 mg/mL remdesivir solution with sufficient volume to allow withdrawal of 20 mL.
The composition of the drug product is adequately described, qualitatively and quantitatively.
Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process.
The manufacturing process is described narratively and in sufficient detail, taking into account pharmaceutical development data. Batch manufacturing formulas and in-process controls are included.
The drug product specification covers appropriate parameters for this dosage form and includes relevant physicochemical, identification, assay and purity tests. They allow for proper control of the finished drug product. The control methods are validated according to international guidelines. Batch data show consistent quality of the drug product.
The drug product is supplied as a sterile product in a single-use, type I clear glass vial. Each vial is sealed with an elastomeric closure and an aluminium overseal with a flip-off cap.
Appropriate stability data have been generated in the packaging materials intended for commercial use and following relevant international guidelines. An in-use stability study has been performed. The data show good stability of the finished product and support the proposed shelf life.

Drug Product: Concentrate for solution for infusion
The finished product (concentrate for solution 5 mg/mL) is a sterile, preservative-free, clear, colourless to yellow solution for dilution in intravenous infusion fluids available in 20 mL vials.
Each 20 mL vial contains sufficient volume to allow withdrawal of 20 mL of sterile solution containing 100 mg of remdesivir.
The composition of the drug product is adequately described, qualitatively and quantitatively.
Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process.
The manufacturing process is described narratively and in sufficient detail, taking into account pharmaceutical development data. Batch manufacturing formulas and in-process controls are included.
The drug product specification covers appropriate parameters for this dosage form and includes relevant physicochemical, identification, assay and purity tests. They allow for proper control of the finished drug product. The control methods are validated according to international guidelines. Batch data show consistent quality of the drug product.
The drug product is supplied as a sterile product in a single-use, type I clear glass vial. Each vial is sealed with an elastomeric closure and an aluminium overseal with a flip-off cap.
Appropriate stability data have been generated in the packaging materials intended for commercial use and following relevant international guidelines. An in-use stability study has been performed. The data show good stability of the finished product and support the proposed shelf life.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and both drug products has been demonstrated.

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5 Nonclinical Aspects

The applicant submitted a comprehensive nonclinical study package to support the marketing authorisation application for Veklury. In addition to the submitted studies, Division Preclinical Review also considered the EMA CHMP assessment report (EMA/CHMP/311666/2020) for the nonclinical safety evaluation.

Pharmacology

Remdesivir (RDV) is the prodrug of a nucleoside analogue, GS-441524, which is intracellularly metabolised to the pharmacologically active nucleoside triphosphate metabolite GS-443902. GS-443902 acts as an analogue of ATP. It competes with the natural ATP substrate to be incorporated into viral RNA, leading to a delayed RNA chain termination. The mode of action characterises RDV as a direct-acting antiviral compound. GS-443902 showed no inhibitory activity towards human DNA or RNA polymerases tested at concentration up to 200 µM. The metabolite was also a poor substrate for human mitochondrial DNA and RNA polymerases. RDV inhibited the *in vitro* replication of SARS-CoV-2 and SARS-CoV in primary human airway epithelial cells with EC_{50} values of 0.0099 µM and 0.0066 µM. Cytotoxicity was low (CC_{50} > 10 µM) with a selectivity index (CC_{50}/EC_{50}) > 1000. RDV, GS-466547 (1:1 diastereomeric mixture of RDV), and GS-441524 also inhibited Ebola virus replication in several cell types with low levels of toxicity.
When administered intravenously to rhesus macaque monkeys at doses of 10/5 mg/kg, RDV reduced clinical signs of a SARS-CoV-2 infection and lung pathology concomitant with lower viral RNA levels in lung tissue upon necropsy.

Secondary pharmacology investigations showed no significant binding of GS-441524 or GS-466547 at any of the 87 targets tested at 10 µM concentration.

Regarding safety pharmacology, no effects on respiratory or central nervous systems were observed in rats at exposure levels corresponding to 2- and 18-fold human exposure, and no effect was seen on cardiovascular system in cynomolgus monkeys at exposure levels corresponding to 2.5-fold the clinical exposure.

Pharmacokinetics

Pharmacokinetic parameters after IV administration in both rats and monkeys were characterised by rapid absorption and elimination (with a half-life ($t_{1/2}$) of 0.29 h) from plasma for RDV and the intermediate metabolite, GS-704277, whereas the nucleoside analogue GS-441524 had a terminal $t_{1/2}$ of 6.21 h in rats, 7.16 h in cynomolgus monkeys, and 8.55 h in rhesus monkeys. Hydrolysis was the major metabolic pathway. GS-441524 was the major compound observed in plasma in all tested animals. No accumulation of RDV or GS-441524 was observed after multiple doses of RDV. IV administration of RDV resulted in efficient formation and highly persistent levels of the pharmacologically active triphosphate GS-443902 in peripheral blood mononuclear cells (PBMCs) with terminal elimination $t_{1/2}$ of approximately 14 h in rhesus monkeys.

The mean free fraction of RDV in human plasma was 12.1%. While RDV was preferentially excluded from the blood cellular fraction, GS-441524 showed modest association with the cellular fraction. Quantitative whole body autoradiography (QWBA) demonstrated similar tissue distribution after a single IV dose of [^{14}C]-RDV at 10 mg/kg in male non-pigmented (SD) and pigmented (LE) rats. [^{14}C]-RDV-derived radioactivity was widely distributed to most of the tissues by the first collection time point. In SD rats, radioactivity was still quantifiable in kidney, liver, and non-pigmented skin at 168 hours postdose. Brain penetration was minimal. The QWBA in LE rats suggested no binding of melanin in the pigmented uveal tract and pigmented skin.
No placental transfer studies were performed.
In mouse, rat, monkey, and human hepatocytes, major RDV-derived metabolites were GS-704277, GS-441524, and GS-441524-phosphate. All human metabolites were found in animals. The human specific metabolite M27, accounting for more than 10% in human plasma at therapeutic dose, is yet to

be identified. The lack of information on M27 was accepted due to the COVID-19 pandemic. The applicant was asked to characterise M27 as a post-marketing commitment.

The routes and extent of RDV excretion were determined after IV administration of 10 mg/kg [^{14}C]RDV to SD rats, rabbits, and cynomolgus monkeys. Renal elimination was the major route of excretion in rats, rabbits and humans, while renal and biliary elimination were the major routes of excretion in cynomolgus monkeys.

Toxicity
Repeat-dose toxicity studies with RDV using IV injections (slow bolus) were conducted in rats, cynomolgus and rhesus monkeys (up to 50, 10, and 20 mg/kg/day, respectively), with a maximum treatment duration of four weeks. Administration route and dosing frequency are consistent with the proposed clinical use. The duration of the repeat-dose toxicity studies supports the intended short-term clinical use (not more than 10 days).

Two female rats treated with 10 mg/kg/day died prematurely. Clinical observations prior to death included pale body and/or ears and eyes, laboured respiration, piloerection, ataxia, tremors or convulsions. Compound-related morbidity was noted in a rhesus monkey treated with 20 mg/kg/day, which was attributed to RDV-related kidney pathology.
The main target organ of toxicity was the kidney in rats and monkeys. In rats, at ≥ 3 mg/kg/day, changes in urinary parameters (increases in creatinine, total protein, N-acetyl-beta-glucosaminidase, cystatin C, beta-2-microglobulin, and kidney injury marker-1) were observed. RDV-related microscopic findings at these doses included basophilic tubules and karyomegaly, associated with increased kidney weights for males. Compound-related increased incidence and severity of chronic progressive nephropathy were noted in recovery male rats. The plasma exposure of rats at 3 mg/kg/day was 0.2-fold the clinical exposure.
Dose-dependent nephrotoxicity was also observed in rhesus monkeys at all doses (5, 10, and 20 mg/kg/day in a 7-day study with 10-day recovery period). Findings consisted of increased serum urea nitrogen and increased creatinine, with correlating histopathology findings of renal tubular atrophy, basophilia, and casts. A NOAEL could not be established. The clinical significance of the nephrotoxicity noted in animal species needs to be carefully monitored in the clinic.

RDV and GS-441524 were negative in bacterial reverse mutation assays. In a chromosome aberration assay in human PBMCs, RDV showed an equivocal response after metabolic activation and was negative without metabolic activation. RDV was negative in an *in vivo* micronucleus test in rats up to doses of 50 mg/kg/day.

No carcinogenicity studies have been performed as RDV is indicated for short-term use only.

No adverse effects of RDV on male reproductive performance were seen in rats. In the fertility and early embryonic toxicity study in females, a significant reduction in the number of corpora lutea, implantation sites and viable embryos, as well as lower mean ovary and uterus/cervix/oviduct weights were noted at doses above 3 mg/kg/day. Thus, the NOAELs for male and female fertility were 10 and 3 mg/kg/day, respectively, associated with plasma exposures of approximately 2-fold and 0.3-fold the clinical exposure. There were no effects of RDV on embryo-foetal development observed in rats and rabbits. The NOAEL was 20 mg/kg/day in both studies, associated with plasma exposures that were about 4-fold the clinical exposure.
In the pre- and postnatal development study in rats, no adverse effects were noted at the highest dose level (10 mg/kg/day). RDV could not be detected in the blood of rat dams and pups. Exposure to GS-441524 was shown for rat pups on postnatal day 10. C_{max} levels of GS-441524 were higher in maternal rats than in pups (up to 143-fold). Milk transfer of GS-441524 can therefore be assumed.
No juvenile toxicity studies were performed. This is in line with EMA PIP for RDV.

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In general, because of low exposure levels of RDV and its metabolites in comparison to the clinical exposure and the existence of the as yet unidentified human major metabolite M27, the overall conclusions regarding the toxicity package must currently be regarded as incomplete. Due to the COVID-19 pandemic situation, these studies were requested to be submitted as post-approval commitments.

In local tolerance tests in rats and monkeys and repeat-dose studies in monkeys, no RDV-related reactions at injection sites were observed.
There are no concerns with regard to excipients and impurities.
Based on the submitted ERA, a final conclusion on the potential risk of RDV to the environment cannot be drawn. The applicant was asked to provide additional studies (post-approval commitment).

Conclusion
Overall, the submitted non-clinical documentation is considered acceptable to support the approval of Veklury with the new active substance remdesivir (RDV) in the proposed indication. The pharmacological properties and the toxicological profile of RDV were well characterised. The safety margins are low or non-existent, which is acceptable in the requested indication and because of the emergency situation related to the COVID-19 pandemic. All nonclinical data that are relevant for safety are adequately included in the information for healthcare professionals.
The applicant was requested to provide status updates on several open issues (incl. metabolite characterisation) as a post-approval commitment.

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6 Clinical and Clinical Pharmacology Aspects

For the clinical pharmacology and clinical assessment, the EMA CHMP assessment report (EMA/CHMP/311666/2020) was also considered.

6.1 Clinical Pharmacology

The pharmacokinetic characteristics of remdesivir and its metabolites were determined in four phase 1 studies in healthy subjects. No data on the PK in the target population are available to date.

ADME

Absorption and biopharmaceutical development

Throughout the clinical programme, a solution and a lyophilised powder formulation were administered, which resulted in comparable plasma levels of remdesivir and its metabolites. The final to-be-marketed drug products are supplied either as 5 mg/mL solution for dilution in intravenous infusion fluids or as lyophilised powder for reconstitution. Each vial contains 100 mg of remdesivir. In view of the intravenous administration, the bioavailability is complete.

Maximal remdesivir plasma concentrations were reached at the end of an infusion, followed by the sequential appearance of the metabolites GS-704277 and GS-441524 after 0.75 h and 1.5 h to 2 h, respectively, and the metabolite GS-443902 in PBMCs after 6 h.

Dose proportionality

Exposures to remdesivir and its metabolites GS-704277 and GS-441524 increased approximately proportionally to the dose across the dose range of 3 mg to 225 mg.

Pharmacokinetics after multiple dosing

No accumulation was observed for remdesivir in plasma, whereas the metabolites GS-441524 and GS-704277 displayed limited accumulation. In PBMCs accumulation for GS-441524 was markedly higher with ratios of up to 3.5. GS-704277 and GS-441524 were estimated to reach steady-state at Day 1 and Day 4, respectively.

Distribution

Protein binding was found to be moderate for remdesivir (87.9%) and low for the metabolites GS-704277 and GS-441524 (1% and 2%, respectively) based on *in vitro* experiments at concentrations below clinically relevant exposures. In addition, no *in vivo* protein binding data are available. Further investigations are therefore warranted to address these issues (*Zulassungsauflagen*).

The volume of distribution of remdesivir was estimated to be 93 L. The mean remdesivir blood-to-plasma ratio increased following intravenous administration (from 0.68 at 15 min to 1.0 at 5 h from the start of infusion). These findings, together with pre-clinical data, indicate that remdesivir and its metabolites are distributed into tissues with an additional association of the metabolites to cellular blood components.

Metabolism

The metabolism of remdesivir to the major metabolites GS-704277 and GS-441524 occurs predominantly by hydrolysis mediated by unidentified hydrolytic enzymes. In addition, CYP2C8, CYP2D6 and CYP3A4 are thought to be involved to a lesser extent in the remdesivir metabolism.

As a result of extensive metabolism of remdesivir, GS-441524 was the predominant entity in plasma (44.2%) followed by remdesivir and the unknown metabolite M27, accounting for 14.2% and 10.6%, respectively. The pharmacologically active metabolite GS-443902 is formed through the intracellular metabolism of GS-441524.

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Further investigations are necessary to characterise the metabolism of remdesivir and the structure of the unknown metabolite M27 (*Zulassungsauflagen*).

Elimination
Renal excretion was the major route of elimination with a minor contribution by the hepatic route (74% vs. 18% of the total radioactive dose). Metabolite GS-441524 was the predominant moiety in urine (48.6% of the total radioactive dose), with 10.3% attributed to unchanged remdesivir; further metabolites were present in smaller amounts. In faeces, desamino-hydroxy-GS-441524 was the major metabolite (11.9%).

The median terminal half-lives of remdesivir, GS-704277, and GS-441524 were calculated to be approximately 1 h, 1.3 h, and 2 h, respectively.

Special Populations
No dedicated studies were conducted to investigate the impact of hepatic and renal impairment on the PK of remdesivir. In addition, the impact of intrinsic factors such as race, age, gender or weight was not evaluated in clinical studies. Furthermore, no population PK analysis was conducted to estimate the variability of the PK of remdesivir based on demographic factors. No paediatric PK data are currently available.

Further investigations are warranted to fill these current gaps in knowledge in order to provide appropriate dosing recommendations in special populations (*Zulassungsauflagen*).

Interactions
Currently, no dedicated *in vivo* drug-drug interaction studies are available to characterise the interaction potential of remdesivir as a victim or a perpetrator.

In *in vitro* experiments, remdesivir was shown to be a substrate of CYP2C8, CYP2D6, and CYP3A4. Furthermore, *in vitro* data suggest that remdesivir is a substrate of P-gp and OATP1B1, but not of BCRP and OATP1B3; OAT1, OAT3, or OCT2 were not investigated.

Remdesivir, but not GS-441524 and GS-7042, was shown to be an *in vitro* inhibitor of CYP2B6 (IC_{50} 77.8 µM), CYP2C8 (IC_{50} 54.9 µM), CYP2C9 (IC_{50} 63.3 µM), CYP2C19 (IC_{50} 68.3 µM), CYP2D6 (IC_{50} 73.0 µM), and CYP3A4 (IC_{50} 1.6 µM). Information on time-dependent CYP inhibition by remdesivir was inconclusive.

Remdesivir was shown to be an inducer of CYP1A2 and, potentially, of CYP3A4. GS-704277, but not GS-441524, was found to be an inducer of CYP1A2, CYP2B6 and CYP3A4.

Remdesivir-mediated inhibition was observed for UGT1A1 (IC_{50} 1.5 µM), UGT1A3 (IC_{50} 3.8 µM), UGT1A4 (IC_{50} 5.9 µM), UGT1A9 (IC_{50} 36.1 µM), and UGT2B7 (IC_{50} 16.2 µM), but not for UGT1A6, whereas no GS-441524- or GS-704277-mediated inhibition of these UGTs was identified.

Remdesivir was shown to be an inhibitor of OATP1B1 (IC_{50} 2.8 µM), OATP1B3 (IC_{50} 2.1 µM), BSEP (IC_{50} 22 µM), and MRP4 (IC_{50} 5.1 µM) *in vitro*, but not of P-gp, BCRP, MRP2, or NTCP; OAT1, OAT3 or OCT2 were not investigated. GS-441524 and GS-704277 did not inhibit BCRP, BSEP, MRP2, MRP3, MRP4, or NTCP at clinically relevant concentrations.

The potential of remdesivir as a victim is considered to be low in view of the moderate-to-high hepatic extraction ratio of remdesivir, the 11% contribution of renal clearance to the systemic clearance, and the intravenous administration. In view of the DDI risk of remdesivir as perpetrator identified *in vitro*,

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potential PK interactions with substrates of CYP3A, OATP1B1, and OATP1B3 should be investigated *in vivo*.

The drug-drug interaction potential posed by the metabolites, particularly the unidentified metabolite M27, is insufficiently characterised.

These gaps in knowledge are currently considered adequately addressed by the wording in the information for healthcare professionals and the *Zulassungsauflagen* to be undertaken.

Pharmacodynamics
Remdesivir is a prodrug of the modified adenine nucleoside analogue GS-441524. Eventually, remdesivir is converted to the pharmacologically active adenosine nucleoside triphosphate analogue GS-443902 in multiple cell types relevant for CoV replication, which leads to delayed RNA chain termination during viral replication due to the incorporation of GS-443902 into nascent RNA chains by the viral RNA-dependent RNA polymerase.

A concentration-QT analysis was conducted using data from heathy volunteers receiving daily doses of 150 mg remdesivir for up to 14 days. The upper bounds of the two-sided 90% confidence intervals of the predicted mean time-matched, baseline-adjusted, placebo-corrected QTcF (ΔΔQTcF) for remdesivir, GS-441524, and GS-704277 were below the regulatory threshold of 10 msec. However, in view of methodological shortcomings in the model development and evaluation and the absence of supra-therapeutic doses, this analysis is of limited relevance, and the absence of an unacceptable prolongation in cardiac repolarisation cannot be entirely excluded.

Further investigations are necessary to characterise the relationship between remdesivir concentrations and QT/QTc interval prolongation (*Zulassungsauflagen*).

6.2 Dose Finding and Dose Recommendation

No dose-finding studies with Veklury were performed. The dose used in the pivotal studies GS-US-540-5776, GS-US-540-5773 and GS-US-540-5774 was selected based on efficacy data from studies in SARS-CoV-2- and MERS-CoV-infected rhesus monkeys and PK bridging from animal data to human doses. The selected dosing schedule was eventually the same as that used in clinical studies for the treatment of Ebola virus disease.

Following a single RDV 200 mg dose or multiple doses of RDV 100 mg, the intracellular trough concentrations of the active triphosphate metabolite GS-443902 in human PBMCs exceeded the EC50 (half-maximal effective concentration) against SARS-CoV-2 in human airway epithelial cells. These concentrations were also comparable to those observed following the doses associated with efficacy in SARS-CoV-2- and MERS-CoV-infected rhesus monkey models.

It is reassuring that the intracellular trough concentrations of the metabolite with the chosen dose are widely above the *in vitro* EC50 against SARS-CoV-2. However, the approach used to determine an adequate dose for the clinical studies did not take into account a potential effect from SARS-CoV-2-infection or COVID-19 on the PK of remdesivir, as no pharmacokinetic data from patients with COVID-19 are currently available.

The optimal duration of therapy with remdesivir was not evaluated prior to the start of the clinical studies. Patients were treated for up to 10 days in studies CO-US-540-5776 and -5758, and a 5-day and 10-day treatment duration were compared in studies CO-US-540-5773 and CO-US-540-5774.

Taken together, the lack of pharmacokinetic data from patients with COVID-19 or with SARS-CoV-2 infection, the lack of comparison with other dose regimens, and the results of remdesivir treatment at the proposed dose in the pivotal studies, leave the possibility that a different dose regimen might be more efficacious and/or result in a better safety profile.

Paediatric dosing

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No PK data from healthy adolescents or from adults or adolescents with SARS-CoV-2-infection or COVID-19 were available at the time of submission. Furthermore, no data on efficacy and safety of remdesivir in the treatment of COVID-19 in patients ≥12 to <18 years of age were available from submitted clinical studies. Comparable exposures and efficacy in adolescents and adult COVID-19 patients at the proposed dose could, therefore, not be confirmed. The available data do not allow dose recommendations to be made for paediatric patients.

6.3 Efficacy

The efficacy of remdesivir in the treatment of COVID-19 was evaluated in four studies. No Clinical Study Report (CSR) was submitted for any of the studies (*Zulassungsauflagen*).

Pivotal studies

CO-US-540-5776 (ACTT-1) was a multicentre, adaptive, randomised, double-blind, placebo-controlled study to evaluate the safety and efficacy of remdesivir in hospitalised patients with COVID-19 and evidence of lower respiratory tract infection. Disease severity ranged from mild/moderate to severe/critically ill.

Subjects were randomised in a 1:1 ratio to receive either remdesivir at 200 mg IV loading dose on Day 1 followed by 100 mg once-daily IV maintenance dose while hospitalised for up to a 10 days, or matching placebo at the same dose and schedule. Both treatments were given in addition to supportive care according to the standard of care for the trial site hospital. Randomisation was stratified by site and severity of illness at enrolment:

severe disease:	requiring mechanical ventilation, requiring oxygen, oxygen saturation SpO2 ≤ 94% on room air, or tachypnoea [respiratory rate ≥ 24 breaths/min];
mild-moderate disease:	SpO2 > 94% and respiratory rate < 24 breaths/min without supplemental oxygen).

Results

Of the 1063 randomised patients, 541 were assigned to the remdesivir group and 522 to the placebo group. The mean age of the patients was 58.9 years, with 36.2% aged >65 years, and 64.3% were male. Overall, 53.2% of the patients were white, 20.6% were black, and 12.6% were Asian. Median time (IQR) from symptom onset to randomisation was 9 (6-12) days and comparable between treatment arms. The majority of patients (88.7%) had severe disease. Somewhat more patients in the remdesivir group had comorbid conditions known to be risk factors for severe course of disease, most notably coronary artery disease, chronic oxygen requirement, and chronic kidney disease. More patients in the placebo group had a score of 7 (hospitalised, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation [ECMO]) on the ordinal scale, indicating more severe disease and a higher risk of adverse outcome. At the time of the analysis, less than half of the patients in each treatment group received the planned full 10-day treatment course due to recovery, death, discontinuation, missed doses during treatment and the fact that about 20% of the patients were still receiving treatment. The results may, therefore, not be fully representative of a 10-day treatment duration.

Superiority of remdesivir over placebo was demonstrated for the primary and key secondary endpoints. Patients in the remdesivir group had a shorter time to recovery than patients in the placebo group (median, 11 days, as compared with 15 days; rate ratio for recovery 1.32 [1.12 to 1.55]; P<0.001; 1059 patients). This primary endpoint was in line with the recommendations in the FDA guideline, although there is currently no single approved endpoint for the evaluation of efficacy in the treatment of COVID-19. A more objective endpoint such as all-cause mortality would have been preferred to rule out any interference of potential problems regarding study conduct. The primary endpoint did not take into account durability of recovery.

For the primary endpoint, the effect was not consistent across disease severity strata; superiority over placebo was only demonstrated in the stratum of severe disease. There was considerable variation in disease severity in the group of patients categorised as having ‘severe disease’ (ranging from requiring supplemental oxygen to mechanical ventilation, including ECMO). A statistically significant

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benefit of remdesivir over placebo in the rate ratio for recovery was only seen in patients with a baseline category 5 score (receiving oxygen). These results should, however, be interpreted with caution, as the study was not powered for such subgroup analyses and no corrections for multiplicity were made. No difference in mortality was observed between the remdesivir and placebo treatment group.

Taken together, the results indicate a beneficial effect of remdesivir in the treatment of COVID-19. The findings suggest that a benefit may be restricted to patients requiring supplemental oxygen but without a need for high-flow oxygen, mechanical ventilation or ECMO, which is in line with the indication applied for.

The results from the ACTT-1 study were not confirmed in another double-blind, randomized, placebo-controlled trial conducted in China (**CO-US-540-5758**). This study was terminated before completion, because of decreasing incidence of COVID-19 in China during the study. No difference in mortality at day 28 was seen between remdesivir- and placebo-treatment, however no reliable conclusions can be drawn due to the early termination of the study.

Studies **GS-US-540-5773** and **GS-US-540-5774** were two randomised, open-label, multicentre studies to evaluate the efficacy of two remdesivir regimens in participants with severe (GS-US-540-5773) or moderate (GS-US-540-5774) COVID-19 infection. In GS-US-540-5773, standard of care therapy together with remdesivir at the dose applied for (single 200 mg IV loading dose on day 1, 100 mg once-daily IV maintenance dose) for either 5 days or 10 days total treatment duration were compared, while study GS-US-540-5774 compared standard of care (SOC) therapy with remdesivir for 5 or 10 days with standard of care alone.

The study enrolled hospitalised patients 18 years of age, or aged ≥12 and <18 years of age weighing ≥40 kg with laboratory-confirmed SARS-CoV-2 infection and with radiographic infiltrates by imaging study. Furthermore, in GS-US-540-5773, patients with severe disease were enrolled: either SpO2 ≤94% on room air or requiring supplemental oxygen. In GS-US-540-5774, patients with moderate disease were enrolled: SpO2 >94% on room air.

The primary endpoint in the studies was clinical status assessed by a 7-point ordinal scale on Day 14 in GS-US-540-5773 and on Day 11 in GS-US-540-5774. The endpoint was not objective as determining the score on the ordinal scale partly involved investigators' individual assessment of patient's clinical status and may also be influenced by hospitals' procedures for the management and discharge of these patients. Together with the open-label design this might have introduced bias and had an influence on the study outcomes. For both studies, and in particular in patients with more severe COVID-19, it can be questioned whether the time period over which the primary endpoint was evaluated was long enough.

Results GS-US-540-5773

The mean age of patients was 60.0 (14.8) years (range 20-98 years), and 63.7% were male. Of note, although adolescents could be enrolled in the study, no participants <18 years of age were included. The majority of participants was white (70.4%), black (11.2%) or Asian (11.5%). The treatment groups were balanced in terms of demographic characteristics but not baseline disease characteristics. Greater proportions of patients in the 10-day group were in the two baseline ordinal scale categories indicating most severe disease as compared to the 5-day group. Median time (IQR) from symptom onset to start of treatment was 8 (5-11) days and 9 (6-12) days in the 5- and 10-day groups, respectively.

After adjustment for imbalances in baseline clinical status, patients receiving a 10-day course of remdesivir had a similar distribution across ordinal categories of clinical status, suggesting that there is no difference in the effect of 5- or 10-day treatment. Numerically, patients in the 10-day treatment group seemed to have worse outcomes as compared to patients in the 5-day treatment group. This was consistent in the secondary endpoints. Because of the uncontrolled, open-label design, this study provides no information on a treatment effect of remdesivir.

Results GS-US-540-5774

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The mean age of patients was 56.0 (15.1) years. Slightly more patients ≥75 years of age were included in the 10-day treatment group. One patient <18 years (12 years old) was included. Of the participants, 61.1% were male, and 61.3% of the patients were white, 18.5% were black, and 19.1% were Asian. Median time (IQR) from symptom onset to start of treatment was 8 (5-11) days and comparable across treatment groups. A slight imbalance in baseline disease characteristics was seen, as more patients in the SOC group required high- or low-flow oxygen.

There was a statistically significant difference in the distribution in clinical status at Day 11, indicating a benefit of remdesivir in participants receiving a 5-day course of remdesivir compared with those receiving SOC alone, while participants receiving a 10-day course of remdesivir had a similar distribution as those receiving SOC alone. Numerically, the outcomes in the 10-day treatment group seemed to be worse than in the 5-day treatment group, as also seen in study GS-US-540-5774. The reasons for this finding are currently unclear. As only 37.8% in the 10-day group received a full course of treatment it is questionable whether the data from the 10-day treatment group are representative for 10 days treatment duration. This further complicates the interpretation of the findings.

6.4 Safety

The safety profile of remdesivir is based on data from 1936 individuals who received at least 1 dose of IV remdesivir, including 1630 with Covid-19; 175 with Ebola virus disease (EVD); and 131 healthy participants in the Phase 1 studies.

The available data from studies CO-US-540-5776 (placebo-controlled) and GS-US-540-5774 (SOC-controlled) indicated no major safety issues. The information for healthcare professionals includes warnings and recommendations for monitoring in relation to potential transaminase elevations and renal impairment. More detailed information on the safety profile and tolerability of remdesivir will become available when the final CSRs and a final safety analysis of all available safety data from the submitted studies will be provided (*Zulassungsauflagen*).

The main findings from the submitted studies were:

CO-US-540-5776

Non-serious Grade 3 or 4 AEs occurred at a similar frequency in the remdesivir arm (28.8%) as in the placebo arm (33.0%). The most common adverse events in the remdesivir group were anaemia or decreased haemoglobin (7.9%, placebo 9.0%); acute kidney injury, decreased estimated glomerular filtration rate or creatinine clearance, or increased blood creatinine (7.4%, placebo 7.3%); pyrexia (5.0%, placebo 3.3%); hyperglycaemia or increased blood glucose level (4.1%, placebo 3.3%); and increased aminotransferase levels including alanine aminotransferase, aspartate aminotransferase, or both (4.1%, placebo 5.9%). No information is available on the relationship to study drug.

Serious adverse events occurred in 114 patients (21.1%) in the remdesivir group and 141 patients (27.0%) in the placebo group. The most frequently reported serious AEs in the remdesivir group were respiratory failure (5.2%), acute respiratory failure (1.7%), respiratory distress (1.7%), cardiac arrest (1.1%), septic shock (1.1%), and uncoded (3.5%). All of these were slightly more common among patients in the placebo group. Four events (two in each group) were judged by site investigators to be related to remdesivir or placebo. No deaths were considered to be related to treatment assignment, as judged by the site investigators.

GS-US-540-5773

A slightly worse safety profile was seen with 10 days treatment as compared to 5 days treatment, potentially as a result of more severely ill patients being included in the 10 day-treatment group. A difference between treatment groups was less pronounced in the first 5 days of treatment.

The most common AEs were

- remdesivir for 5 days: nausea (10.0%), constipation (6.5%), and acute respiratory failure (6.0%)
- remdesivir for 10 days: acute respiratory failure (10.7%); nausea (8.6%); and ALT increased and acute kidney injury (7.6% each)

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The most common drug related AEs were nausea (3.5%), ALT increased (4.3%), AST increased (3.5%), and transaminases increased (2.0%). These occurred somewhat more often with 10 days treatment as compared to 5 days treatment.

The most common serious AEs were acute respiratory failure (7.1%), coronavirus infection (4.3%), respiratory failure (3.8%), respiratory distress (1.8%), and septic shock (1.8%). All of these were slightly more common in the 10-day treatment group, with the most notable difference being observed for acute respiratory failure (5-day group 5.0% vs. 10-day group 9.1%). All of the serious AEs considered to be drug-related can be grouped as hepatic enzymes increased (5-day group 1.5% vs. 10-day group 2.0%).

Overall, 44 deaths were reported; 19 (9.5%) in the RDV 5-day group and 25 (12.7%) in the RDV 10-day group, with acute respiratory failure and multi-organ failure being the most frequently reported causes of death.

AEs leading to study drug discontinuation were more often reported in the 10-day treatment group compared to the 5-day treatment group and were mostly related to increases in hepatic enzymes. In the 10-day treatment group, patients also discontinued study drug due to acute kidney injury (2.5%, 5 patients).

GS-US-540-5774

It should be noted that only 37.8% of the patients in the 10-day treatment group received a full 10 days of treatment. Almost half of the patients in this group did not receive more than 5 days of treatment. Therefore, the safety findings in the 10-day treatment group are not fully representative of 10 days treatment duration.

Overall, AEs were reported in 50.8% of patients in the 5-day treatment group, in 54.9% of patients in the 10-day treatment group, and 45.0% of patients in the SOC group.

The most common AEs were

- remdesivir for 5 days: nausea (9.9%), headache (5.2%), and diarrhoea (5.2%)
- remdesivir for 10 days: nausea (9.3%), hypokalaemia (6.7%), and diarrhoea (5.2%)
- SOC: diarrhoea (7.0%), constipation (4.5%), and insomnia and pyrexia (each 3.5%)

More drug-related AEs were reported in the 5-day treatment group as compared to the 10-day treatment group. The most common drug-related AEs were nausea (5-day 6.8%; 10-day 3.6%), ALT increased (5-day 3.7%; 10-day 1.6%), AST increased (5-day 2.6%; 10-day 1.6%), rash (5-day 2.6%; 10-day 0.5%), headache (5-day 2.1%; 10-day 1.6%), and hypertransaminasaemia (5-day 1.0%; 10-day 2.1%).

Serious AEs were more frequently reported in the standard of care group as compared to the remdesivir groups. No event was reported in >1 participant in either remdesivir group, with no notable pattern. One serious AE of heart rate decreased in the remdesivir 5-day treatment group was considered to be drug-related.

Unlike in study GS-US-540-5773, in study GS-US-540-5774 no clear difference was observed in the frequency and severity of the AEs between the different treatment durations.

Overall, 8 deaths were reported; two (1.0%) in the remdesivir 5-day group, two (1.0%) in the remdesivir 10-day group, and four (2.0%) in the SOC group, with COVID-19 and respiratory failure being the most frequently reported causes of death.

AEs leading to study drug discontinuation were slightly more often reported in the 10-day treatment group compared to the 5-day treatment group. In the 10-day treatment group, study drug discontinuation was mostly due to AEs related to increases in hepatic enzymes, while in the 5-day treatment group this was due to AEs of ALT increased (0.5%), heart rate decreased (0.5%), and rash (1.0%).

Grade 3 or 4 laboratory abnormalities were reported in 12.8%, 16.2% and 17.7% of patients in the remdesivir 5-day group, remdesivir 10-day group and SOC group, respectively. Platelets decreased, white blood cells (WBC) decreased, hyperglycaemia, and hyperbilirubinaemia occurred somewhat more often in the remdesivir groups.

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6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Coronavirus disease 2019 (COVID-19) is the disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). COVID-19 can range from mild to severe disease, with the majority (approximately 80%) having mild to moderate disease, including flu-like symptoms up to mild pneumonia. About 20% of infected patients develop severe to critical disease, with complications including acute respiratory distress syndrome (ARDS), arrhythmia, septic shock, acute cardiac injury, acute coronary syndrome, cardiomyopathy, acute respiratory injury, and acute renal injury (see below for main risk factors for severe disease). At the time of assessment, there were no approved drugs to treat COVID-19 in Switzerland.

The pharmacokinetic profiles of remdesivir and its plasma metabolites GS-441524 and GS-704277, as well as the PBMC-associated, pharmacologically active metabolite GS-443902 following the proposed dosing regimen were characterised in four phase 1 studies.

No data on the PK in the target population are available to date. No clinical studies investigating the impact of hepatic and renal impairment on the PK of remdesivir and its metabolites were conducted. The impact of other factors such as race, age, gender or weight on the PK of remdesivir and its metabolites was not evaluated in the context of clinical studies. Furthermore, no population PK analysis was conducted to estimate the variability of the PK of remdesivir based on demographic factors.

The dose applied for was selected based on efficacy data from studies in SARS-CoV-2- and MERS-CoV-infected rhesus monkeys and PK bridging from animal data to human doses. A potential effect from SARS-CoV-2 infection or COVID-19 on the PK of remdesivir was not taken into account, as no PK data in the target population are currently available. Based on the limited available information, it cannot be ruled out that another dose regimen might be more efficacious and/or result in a better safety profile.

The optimal duration of therapy with remdesivir was not evaluated prior to the start of the clinical studies. 5-day and 10-day treatment durations were compared in studies CO-US-540-5773 and CO-US-540-5774. Results indicated possibly worse outcomes with 10-day treatment duration. The reasons for this are currently unclear. However, due to the subjective endpoint used and the open-label design, no reliable conclusions on the optimal treatment duration can be drawn from these studies.

Simulations based on the PBPK model suggest that the proposed dose results in similar remdesivir and GS-441524 steady-state exposures in adolescents compared to those in adults. However, considering the shortcomings of the model development and evaluation, this could not be reliably concluded. Furthermore, it is currently unclear whether efficacy data from adults can be extrapolated to paediatric patients. As there were no PK or efficacy data available to confirm comparable exposures and/or efficacy in adolescents and adult COVID-19 patients at the proposed dose, no dose recommendation for paediatric patients could be provided.

Remdesivir treatment resulted in a 4-day reduction in time to recovery as compared to placebo treatment in hospitalised patients with COVID-19 infection. Data on efficacy mainly resulted from one placebo-controlled phase 3 study, in which patients received treatment for 10 days. The observed shorter time to recovery compared to placebo was mainly driven by the effect in patients with severe disease, and more specifically by patients with baseline category 5 score (receiving oxygen). This same pattern was observed for clinical status at day 15 and mortality at day 14. These results should, however, be interpreted with caution, as the study was not powered for such subgroup analyses (by disease severity, baseline ordinal scale), and no corrections for multiplicity were made. The results can, at this point be considered suggestive of a beneficial effect in the target population applied for, but ideally would need confirmation from a second adequately designed and conducted randomised controlled trial.

Remdesivir treatment was relatively well-tolerated as compared to placebo; Grade 3 and 4 adverse events and (drug-related) serious adverse events occurred at a similar frequency. In addition, in comparison to SOC, no relevant differences were observed.

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No dedicated *in vivo* DDI studies were conducted. Overall, the DDI assessment was insufficient.

The absence of an unacceptable prolongation in cardiac repolarisation cannot be entirely excluded considering the lack of a tQT study and the shortcomings of the concentration-QT analysis.

The most frequently reported AEs in the RDV group in study CO-US-540-5776 were anaemia or decreased haemoglobin (7.9%, placebo 9.0%); acute kidney injury, decreased estimated glomerular filtration rate or creatinine clearance, or increased blood creatinine (7.4%, placebo 7.3%); pyrexia (5.0%, placebo 3.3%); hyperglycaemia or increased blood glucose level (4.1%, placebo 3.3%); and increased aminotransferase levels including alanine aminotransferase, aspartate aminotransferase, or both (4.1%, placebo 5.9%).

The most frequently reported AEs in the RDV group in studies CO-US-540-5773 and -5774 were nausea, diarrhoea, headache, constipation, acute respiratory failure, ALT increased, acute kidney injury, and hypokalaemia.

Available preclinical data indicate a potential risk for renal toxicity. A similar risk in humans cannot be ruled out.

The available data indicate no major safety issues, and adequate warnings are included in the information for healthcare professionals. More detailed information on the safety profile and tolerability of remdesivir will become available when the final CSRs and a final safety analysis of all available safety data from the submitted studies will be provided.

In view of the unmet medical need for the treatment of patients with COVID-19, the *Zulassungsauflagen*, and the proposed wording in the information for healthcare professionals, the clinical pharmacology package was considered acceptable. There remain uncertainties on the efficacy and safety of remdesivir treatment because, at this stage, mainly preliminary data are available. Nevertheless, available data indicate a benefit of remdesivir and no major safety issues.

It is anticipated that the existing uncertainties can be resolved once more information will become available from final analysis of ongoing studies. Therefore, and in view of the exceptional circumstances due to the current pandemic with a clear unmet medical need, a temporary authorisation in accordance with Art. 9a TPA was granted.

In the context of the temporary authorisation in accordance with Art. 9a TPA, several *Zulassungsauflagen* were defined. In order to confirm currently available results, the final clinical study reports of studies CO-US-540-5776, GS-US-540-5773, and GS-US-540-5774 will be submitted. The specific obligations defined by the EMA/CHMP (EMA/357513/2020) regarding these studies were fully endorsed, and it is anticipated that the final study reports and the responses to the specific obligations will address the existing uncertainties. Therefore, this information was requested to be submitted to Swissmedic as well. Furthermore, the applicant was asked to critically discuss final results of the Solidarity trial in view of the final outcomes of their submitted studies.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order 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. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. 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 occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Veklury, powder for concentrate for solution for infusion and Veklury, concentrate for solution for infusion 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 reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ 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 is temporarily authorised – see "Properties/Effects" section.

Veklury®

Composition

Active substances

Remdesivir

Veklury 100 mg powder for concentrate for solution for infusion

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.

Veklury 100 mg concentrate for solution for infusion

Excipients

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

A 100 mg Veklury dose of concentrate for solution for infusion contains approximately 417.1 mg sodium and 6 g betadex sulfobutyl ether sodium.

Pharmaceutical form and active substance quantity per unit

Veklury 100 mg powder for concentrate for solution for infusion

Powder for concentrate for solution for 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.

Veklury 100 mg concentrate for solution for infusion

Concentrate for solution for infusion (sterile concentrate).
Clear, colourless to yellow, aqueous-based concentrated solution.

Each vial contains 100 mg/20 ml of remdesivir.
Each ml of concentrate contains 5 mg of remdesivir.

Indications/Uses

Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults with pneumonia requiring supplemental oxygen (see “Properties/Effects”).

Dosage/Administration

Use of Veklury is confined to healthcare facilities in which patients can be monitored closely (see section “Warnings and precautions”).

The recommended dosage of Veklury in adults is:

- Day 1 – single loading dose of remdesivir 200 mg given by intravenous infusion over 30 to 120 minutes
- Day 2 onwards – remdesivir 100 mg given once daily by intravenous infusion over 30 to 120 minutes.

Duration of treatment

The total duration of treatment should be at least 5 days and not more than 10 days.

Special dosage instructions

Patients with impaired hepatic function

The pharmacokinetics of Veklury have not been evaluated in patients with hepatic impairment. It is not known if dosage adjustment is appropriate in patients with hepatic impairment (see “Warnings and precautions” and “Pharmacokinetics”).

Patients with impaired renal function

The pharmacokinetics of Veklury have not been evaluated in patients with renal impairment. Patients with an estimated glomerular filtration rate (eGFR) ≥ 30 ml/min have received remdesivir for treatment of COVID-19 with no dose adjustment. Veklury should not be used in patients with eGFR < 30 ml/min (see “Warnings and precautions” and “Pharmacokinetics”).

Elderly patients

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

Paediatric patients

The safety and efficacy of Veklury in children under the age of 18 years have not yet been established. There is insufficient data available.

Mode of administration

Veklury 100 mg powder for concentrate for solution for infusion

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 1: Recommended rate of infusion for reconstituted and diluted Veklury powder for concentrate for solution for infusion

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

Veklury 100 mg concentrate for solution for infusion

For intravenous infusion use.

Veklury is for administration by intravenous infusion after further dilution.

It must not be given as an IM injection.

For instructions on dilution of the medicinal product before administration, see "Instructions for handling".

Table 2: Recommended rate of infusion for diluted Veklury concentrate for solution for infusion

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

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 have been observed during and following administration of Veklury. Signs and symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, 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. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of Veklury and initiate appropriate treatment.

Transaminase elevations

Transaminase elevations have been observed in the Veklury clinical studies, including in healthy volunteers and patients with COVID-19. Liver function should be determined in all patients prior to starting Veklury and should be monitored while receiving it as clinically appropriate. No clinical studies with Veklury have been conducted in patients with hepatic impairment. Veklury should only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk.

- Veklury should not be initiated in patients with Alanine Aminotransferase (ALT) ≥ 5 times the upper limit of normal (ULN) at baseline
- Veklury should be discontinued in patients who develop:
  - ALT ≥ 5 times the ULN during treatment with Veklury. It may be restarted when ALT is < 5 times the ULN.

    OR
  - ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR) (see “Undesirable effects” and “Pharmacokinetics”).

Renal Impairment

In animal studies on rats and monkeys, severe renal toxicity was observed (see “Preclinical data”). The mechanism of this renal toxicity is not fully understood. A relevance for humans cannot be excluded.

All patients should have eGFR determined prior to starting Veklury and while receiving it as clinically appropriate. Veklury should not be used in patients with eGFR < 30 ml/min.

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

Co-administration of Veklury and chloroquine phosphate or hydroxychloroquine sulphate is not recommended based on *in vitro* data demonstrating an antagonistic effect of chloroquine on the

intracellular metabolic activation and antiviral activity of remdesivir (see section “Interactions” and “Properties/Effects”).

Excipients

Veklury contains betadex sulfobutyl ether sodium, which is renally cleared and accumulates in patients with decreased renal function, which may potentially adversely affect renal function. Veklury should not be used in patients with eGFR < 30 ml/min (see “Dosage/Administration” and “Pharmacokinetics”).

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.

A 100 mg Veklury dose of concentrate for solution for infusion contains approximately 417.1 mg sodium , equivalent to 20.9% of the WHO recommended maximum daily dietary intake of 2 g sodium for an adult.

Interactions

No clinical interaction studies have been performed with Veklury. The overall potential for interactions is currently unknown; patients should remain under close observation during the days of Veklury administration. Due to antagonism observed *in vitro*, concomitant use of Veklury with chloroquine phosphate or hydroxychloroquine sulphate is not recommended.

Effect of Veklury on other medicinal products

In vitro, remdesivir is an inhibitor 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 was not studied. The potential for time-dependent inhibition of CYP450 enzymes by remdesivir was not studied.

Remdesivir inhibited OATP1B1 and OATP1B3 *in vitro*. No data is available for OAT1, OAT3 or OCT2 inhibition by remdesivir.

Remdesivir may transiently increase plasma concentrations of medicinal products that are substrates of CYP3A or OATP 1B1/1B3. No data is available, however it can be suggested that medicinal products that are substrates of CYP3A4 or substrates of OATP 1B1/1B3 should be administered at least 2 hours after remdesivir. Remdesivir induced CYP1A2 and potentially CYP3A *in vitro, but not CYP2B6 in vitro.* Co-administration of Veklury with CYP1A2 or CYP3A4 substrates with narrow therapeutic index may lead to loss of their efficacy.

In vitro data indicates no clinically relevant inhibition of UGT1A1, 1A3, 1A4, 1A6, 1A9 or 2B7 by remdesivir or its metabolites GS-441524 and GS-704277.

At physiologically relevant concentrations, remdesivir and its metabolites did not inhibit PgP and BCRP *in vitro.*

Dexamethasone is a substrate of CYP3A4 and although remdesivir inhibits CYP3A4, due to remdesivir's rapid clearance after intravenous administration, remdesivir is unlikely to have a significant effect on dexamethasone exposure.

Effect of other medicinal products on Veklury

In vitro, remdesivir is a substrate for esterases in plasma and tissue, drug metabolising enzymes CYP2C8, CYP2D6, and CYP3A4, and is a substrate for Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and P-glycoprotein (P-gp) transporters.

The potential of interaction of Veklury with inhibitors/inducers of the hydrolytic pathway (esterase) or CYP2C8, 2D6 or 3A4 has not been studied. The risk of clinically relevant interaction is unknown. Strong inhibitors may result in increased remdesivir exposure. The use of strong inducers (e.g. rifampicin) may decrease plasma concentrations of remdesivir and is not recommended.

Dexamethasone is reported to be a moderate inducer of CYP3A and P-gp. Induction is dose-dependent and occurs after multiple doses. Dexamethasone is unlikely to have a clinically significant effect on Veklury as Veklury has a moderate-high hepatic extraction ratio, and is used for a short duration in the treatment of COVID-19.

Pregnancy, lactation

Women of child-bearing potential have to use effective contraception during treatment.

Pregnancy

There are no data from the use of Veklury in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see “Preclinical Data”). Veklury should not be used during pregnancy unless the clinical condition of the women requires treatment with it.

Lactation

It is unknown whether remdesivir is excreted in human milk or the effects on the breast-fed infant, or the effects on milk production.

Because of the potential for viral transmission to SARS-CoV-2 negative infants and adverse reactions from the drug in breast-feeding infants, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Veklury therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No human data on the effect of Veklury on fertility are available. In male rats, there was no effect on mating or fertility with Veklury 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, 4 Phase 3 studies in hospitalized patients with COVID-19, and from hospitalized patients with COVID-19 who received Veklury in a compassionate use program. The most common adverse reaction in healthy volunteers 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 3 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).

Table 3: Tabulated list of adverse reactions

Frequency	Adverse reaction
Immune system disorders	
Rare	hypersensitivity
Nervous system disorders	
Common	headache
Gastrointestinal disorders	
Common	nausea
Hepatobiliary disorders	
Very common	transaminases increased (14%)
Skin and subcutaneous tissue disorders	
Common	rash
Injury, poisoning and procedural complications	
Rare	infusion-related reaction

Description of selected undesirable effects

Transaminases Increased

In healthy volunteer studies, increases in ALT, aspartate aminotransferase (AST) or both in subjects who received Veklury were grade 1 (10%) or grade 2 (4%). In a randomised, double-blind, placebo-controlled clinical study of patients with COVID-19 (NIAID ACTT-1), the incidence of grade ≥ 3 non-serious adverse events of increased aminotransferase levels including ALT, AST, or both was 4% in patients receiving Veklury compared with 6% in patients receiving placebo. In a randomised, open-label multi-centre clinical study (Study GS-US-540-5773) in hospitalised patients with severe COVID-19 receiving Veklury for 5 (n=200) or 10 days (n=197), any grade (≥ 1.25 × ULN) laboratory abnormalities of increased AST and increased ALT occurred in 40% and 42% of patients, respectively, receiving Veklury. Grade ≥ 3 (≥ 5.0 × ULN) laboratory abnormalities of increased AST and increased ALT both occurred in 7% of patients receiving Veklury. In a randomised, open-label multi-centre clinical study (Study GS-US-540-5774) in hospitalised patients with moderate COVID-19 receiving Veklury for 5 (n=191) or 10 days (n=193) compared to standard of care (n=200), any grade laboratory abnormalities of increased AST and increased ALT occurred in 32% and 33% of patients, respectively, receiving Veklury, and 33% and 39% of patients, respectively, receiving standard of care. Grade ≥ 3 laboratory abnormalities of increased AST and increased ALT occurred in 2% and 3% of patients, respectively, receiving Veklury and 6% and 7%, respectively, receiving standard of care.

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 Veklury 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.

Properties/Effects

ATC code

J05A

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

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.

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. 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 normal human bronchial epithelial cells.

Resistance

Cell culture resistance profiling of remdesivir using the rodent CoV murine hepatitis virus identified 2 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 cell culture and attenuated SARS-CoV pathogenesis in a mouse model.

The cell culture development of SARS-CoV-2 resistance to remdesivir has not been assessed to date. No clinical data are available on the development of SARS-CoV-2 resistance to remdesivir.

Clinical efficacy

Clinical Studies in Subjects with COVID-19

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

A randomised, double-blind, placebo-controlled clinical study evaluated Veklury 200 mg once daily for 1 day followed by Veklury 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 Veklury) were

on mechanical ventilation/ECMO. Patients were randomised 1:1, stratified by disease severity at enrolment, to receive Veklury (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 33% (180/541) of the patients received a 10-day treatment course with Veklury.

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 Veklury 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 Veklury 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 Veklury was most apparent in patients receiving oxygen, however, not on ventilation, at Day 1 (rate recovery 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% for the Veklury group vs 15% 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 Veklury for 5 days with 197 patients who received Veklury for 10 days. Patients on mechanical ventilation at screening were excluded. All patients received 200 mg of Veklury 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 hospitalization prior to first dose of Veklury were similar across treatment groups.

Overall, after adjusting for between-group differences at baseline, patients receiving a 5-day course of Veklury 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, recovery rates were 70% and 58%, and mortality rates were 8% and 11%, in the 5-day and 10-day groups, respectively. There were no significant differences once adjusted for between group differences at baseline.

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

A randomized, open-label multi-centre clinical study (GS-US-540-5774) of hospitalized 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 Veklury for 5 days (n=191) and treatment with Veklury for 10 days (n=193) with standard of care (n=200). Patients treated with Veklury 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 hospitalization prior to first dose of Veklury were similar across treatment groups.

Overall, the odds of improvement in the ordinal scale were higher in the 5-day Veklury 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]; p=0.18). At Day 11 observed mortality rates for the 5-day, 10-day, and standard of care groups were 0%, 1%, and 2%, respectively.

QT

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

Temporary authorisation

The medicinal product Veklury has been granted temporary authorisation as the clinical data was incomplete at the time the authorisation application was assessed (Art. 9a TPA). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be transformed into an ordinary authorisation.

Pharmacokinetics

The pharmacokinetic properties of remdesivir have been investigated in healthy volunteers. No pharmacokinetic data is available from patients with COVID-19.

Absorption

The pharmacokinetic properties of remdesivir and the predominant circulating metabolite GS-441524 have been evaluated in healthy adult subjects. Following intravenous administration of Veklury 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% bound to human plasma proteins. Protein binding of GS-441524 was low (2% bound) in human plasma. After a single 150 mg dose of [^{14}C]-remdesivir in healthy subjects, 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 metabolised to the pharmacologically active nucleoside analog triphosphate GS-443902 (formed intracellularly). 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. The human mass balance study also indicates presence of a currently unidentified major metabolite (M27) in 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.

Kinetics in specific patient groups

Age, gender and ethnicity

Pharmacokinetic differences for gender, race, and age have not been evaluated.

Hepatic impairment

The pharmacokinetics of remdesivir and GS-441524 in hepatic impairment has not been evaluated. The role of the liver in the metabolism of remdesivir is unknown.

Renal impairment

The pharmacokinetics of remdesivir and GS-441524 in renal impairment has not been evaluated. Remdesivir is not cleared unchanged in urine to any substantial extent, but its main metabolite GS-441524 is renally cleared and the metabolite levels in plasma may theoretically increase in patients with impaired renal function. The excipient betadex sulfobutyl ether sodium is renally cleared and accumulates in patients with decreased renal function. Veklury should not be used in patients with eGFR < 30 ml/min.

Paediatric patients

The pharmacokinetics in paediatric patients have not been evaluated.

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 at the recommended human dose (RHD). An unidentified major metabolite (M27) was shown to be present in human plasma (see “Pharmacokinetics”). The exposure of M27 in rhesus monkeys and rats is unknown. Animal studies may therefore not be informative of potential risks associated with this metabolite.

Mutagenicity

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.

It is unknown if the active nucleoside analog triphosphate GS-443902 and the unidentified major human metabolite M27 are formed in rats and rabbits. The reproductive toxicity studies may therefore not be informative of potential risks associated with these metabolites.

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

Veklury 100 mg powder for concentrate for solution for infusion

Reconstituted and diluted solution for infusion

Store diluted Veklury solution for infusion up to 4 hours at below 25°C or 24 hours in a refrigerator (2°C to 8°C).

Veklury 100 mg concentrate for solution for infusion

Diluted solution for infusion
Store diluted Veklury solution for infusion up to 4 hours below 25°C or 24 hours in a refrigerator (2°C to 8°C).

Special precautions for storage

Veklury 100 mg powder for concentrate for solution for infusion

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”.

Veklury 100 mg concentrate for solution for infusion

Keep out of reach of children.
Store in the refrigerator (2-8°C).
For storage conditions after dilution of the medicinal product, see “Shelf life”.

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.

1. Veklury 100 mg powder for concentrate for solution for infusion

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.

1.1. Preparation of Veklury solution for infusion

1.1.1. 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.
  - 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.

- 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.

1.1.2. 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.

- Using Table 4, determine the volume of sodium chloride 9 mg/ml (0.9%) solution for injection to withdraw from the infusion bag.

Table 4: 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 4.
- Withdraw the required volume of reconstituted remdesivir powder for concentrate for solution for infusion using an appropriately sized syringe per Table 4. 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 4 hours at room temperature (20°C to 25°C) or 24 hours in the refrigerator (at 2°C to 8°C) (including any time before dilution into intravenous infusion fluids).

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

1.2. Disposal

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

2. Veklury 100 mg concentrate for solution for infusion

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

2.1. Preparation of Veklury solution for infusion

2.1.1. 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.

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

- Allow to warm to room temperature (20°C to 25°C).
- Inspect the vial to ensure the container closure is free from defects and the concentrate for solution for infusion is free of particulate matter.
- Using Table 5, determine the volume of sodium chloride 9 mg/mL (0.9%) to withdraw from the infusion bag.

Table 5: Recommended dilution instructions – Veklury 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 Veklury
200 mg (2 vials)	250 ml	40 ml	2 x 20 ml
100 mg (1 vial)		20 ml	20 ml

- Withdraw and discard the required volume of sodium chloride 9 mg/ml from the bag per Table 5 using an appropriately sized syringe and needle.
- Withdraw the required volume of Veklury concentrate for solution for infusion from the remdesivir vial using an appropriately sized syringe per Table 5.
  - Pull the syringe plunger rod back to fill the syringe with approximately 10 ml of air.
  - Inject the air into the Veklury injection vial above the level of the solution.
  - Invert the vial and withdraw the required volume of remdesivir concentrate for solution for infusion into the syringe. The last 5 ml of solution requires more force to withdraw.
- Discard any unused solution remaining in the Veklury vial.

- Transfer the required volume of remdesivir concentrate for solution for infusion to the infusion bag.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- The prepared diluted infusion solution is stable for 4 hours at room temperature (20°C to 25°C) or 24 hours in the refrigerator at 2°C to 8°C.

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

2.2. Disposal

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

Authorisation number

68026, 68043 (Swissmedic)

Packs

Veklury 100 mg powder for concentrate for solution for infusion: 1 vial (To be used in hospitals only according to Art. 26 para. 4 TPO) [A]
Veklury 100 mg concentrate for solution for infusion: 1 vial (To be used in hospitals only according to Art. 26 para. 4 TPO) [A]

Marketing authorisation holder

Gilead Sciences Switzerland Sàrl, Zug

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