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Date: 19 September 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Veklury

International non-proprietary name: remdesivir
Pharmaceutical form: powder for concentrate for solution for infusion
Dosage strength(s): 100 mg
Route(s) of administration: intravenous
Marketing authorisation holder: Gilead Sciences Switzerland Sàrl
Marketing authorisation no.: 68026
Decision and decision date: approved on 05.04.2023

Note:

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

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CYP	Cytochrome P450
DDI	Drug-drug interaction
ECMO	Extracorporeal membrane oxygenation
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
IMV	Invasive mechanical ventilation
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
QD	Once daily (Latin: quaque die)
RDV	Remdesivir
RMP	Risk management plan
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background information on the procedure

2.1 Applicant's request(s)

Authorisation for a COVID-19 medicinal product
In connection with the COVID-19 pandemic, the applicant requested a rolling submission procedure.

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

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 paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment),
- adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen or hospitalisation for COVID-19 and who are at risk of developing a severe COVID-19 course

(see "Properties/Effects").

2.2.2 Approved indication

Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in
- adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment),
- adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen or hospitalisation for COVID-19 and who are at increased risk of developing a severe COVID-19 course

(see "Properties/Effects").

2.2.3 Requested dosage

Summary of the requested standard dosage:

Table 1: Recommended dose of remdesivir in adults and paediatric patients [1]

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

[1] M2.7.3, Section 4

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Table 2: Treatment duration[2]

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

Mode of administration

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

Infusion bag volume	Infusion time	Rate of infusion
250 ml	30 min	8.33 ml/min
	60 min	4.17 ml/min
	120 min	2.08 ml/min
100 ml	30 min	3.33 ml/min
	60 min	1.67 ml/min
	120 min	0.83 ml/min

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

Infusion bag volume	Infusion time	Rate of infusion[a]
100 ml	30 min	3.33 ml/min
	60 min	1.67 ml/min
	120 min	0.83 ml/min
50 ml	30 min	1.67 ml/min
	60 min	0.83 ml/min
	120 min	0.42 ml/min
25 ml	30 min	0.83 ml/min
	60 min	0.42 ml/min
	120 min	0.21 ml/min

a The rate of infusion may be adjusted based on the total volume to be infused.

[2] M2.7.3, Section 4

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2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	2 August 2022
Formal control completed	9 August 2022
Preliminary decision	18 November 2022
Response to preliminary decision	16 December 2022
Final decision	5 April 2023
Decision	approval

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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 benign to severe, with the majority of patients having mild to moderate disease, including flu-like symptoms up to mild pneumonia. Asymptomatic infections also occur, the exact proportion of which is currently unknown.

Some infected patients develop severe to critical disease with complications including acute respiratory distress syndrome (ARDS), septic shock and various end organ damage (e.g. kidney, heart), some of which as a result of a hyperinflammatory response. Important risk factors for a severe course of the 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 type 2 diabetes mellitus.

SARS-CoV-2 infection and hospitalisation are less frequent in children than in adults. Children more often have asymptomatic infection. In symptomatic cases, children may more frequently have fever and/or gastrointestinal symptoms than adults. Similar to adults, SARS-CoV-2 infection can result in severe and critical disease. Potential risk factors include medically complex conditions (including certain genetic disorders, neurological diseases, and cancer), type 1 diabetes, complex congenital heart disease, and obesity.[3]

Vaccines based on various technologies have been developed for the prevention of COVID-19 and are widely used in Switzerland. The currently available therapeutics in Switzerland, depending on the status of the disease and patients' characteristics, are essentially dexamethasone, baricitinib, remdesivir, and nirmatrelvir/ritonavir. Four monoclonal antibody-based therapeutics have been approved so far: casirivimab/imdevimab (Ronapreve), sotrovimab (Xevudy), regdanvimab (Regkirona), and tixagevimab/cilgavimab (Evusheld). Of these, dexamethasone, casirivimab/imdevimab, sotrovimab, and tixagevimab/cilgavimab are approved for use in patients 12 years and older and weighing at least 40 kg.

[3] Bhimraj A, Morgan RL, Shumaker AH, Baden L, Cheng VC, Edwards KM, Gallagher JC, Gandhi RT, Muller WJ, Nakamura MM, O'Horo JC, Shafer RW, Shoham S, Murad MH, Mustafa RA, Sultan S, Falck-Ytter Y. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America **2022**; Version 10.0.0. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 28 October 2022

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4 Clinical aspects

In addition to the submitted data, the FDA public assessment report and the EMA assessment report (EMEA/H/C/005622/II/0035/G) were considered in the assessment of the clinical data.

4.1 Clinical pharmacology

ADME

Sparse paediatric pharmacokinetic (PK) data to determine the plasma levels of remdesivir and its metabolites GS-441524 and GS-704277 were collected in study GS-US-540-5823.
This was a single-arm, open-label study including participants from birth to <18 years of age with laboratory-confirmed COVID-19. PK data are available for 50 subjects enrolled in one of five cohorts:

- Cohort 1: 12 years to <18 years and ≥40 kg (n=12)
- Cohort 2: 28 days to <18 years and 20 kg to <40 kg (n=12)
- Cohort 3: 28 days to <18 years and 12 kg to <20 kg (n=11)
- Cohort 4: 28 days to <18 years and 3 kg to <12 kg (n=10)
- Cohort 8: <12 years and ≥40 kg (n=5)

Whereas the subjects in cohorts 1 and 8 received the approved adult flat dose (200 mg loading dose followed by 100 mg once daily (QD) for up to 10 days), subjects in cohorts 2 to 4 received a body weight-based dose (5 mg/kg loading dose followed by 2.5 mg/kg QD for up to 10 days).

Generally, the ranges of exposure to remdesivir, GS-441524, and GS-704277 were comparable. However, the variability was significant in all cohorts. These paediatric exposures were compared to PK data from adult participants enrolled in the Phase 3 studies GS-US-540-9012 (outpatients) and CO-US-540-5844 (REMDACTA, hospitalised patients).
Compared to the adults, remdesivir and GS-704277 mean exposures were increased by up to approximately two-fold in paediatric patients, whereas GS-441524 exposures were comparable. However, the variability, particularly in the adult data, was generally significant, and the paediatric exposures were overall within the range of exposure observed in adults. Furthermore, the adult population included data from outpatients, whereas only data from hospitalised children were available.

In view of increased remdesivir exposure, sulfobutylether β-cyclodextrin sodium (SBECD) exposure was determined where possible, since this excipient has been associated with kidney toxicity. No correlation was identified between SBECD paediatric exposure and the seven most frequent adverse events and adverse events involving acute kidney injury that were reported in study GS-US-540-5823.

Special populations

Using data from three adult Phase 1 healthy volunteer and two adult Phase 3 studies as well as the paediatric Phase 2/3 study GS-US-540-5823, a population PK analysis was conducted to identify factors that account for the variability of remdesivir, GS-441524, and GS-704277 PK in adult and paediatric subjects. 654 of the total 14,588 PK samples were from paediatric patients, and only hospitalised children were included.
The PK was described well by sequential 2-compartment models for remdesivir and GS-704277 and by a 3-compartment model for GS-441524. The effect of body weight was included based on fixed allometry by fixing clearance-related body weight exponents at 0.75 and volume of distribution-related body weight exponents at 1.0. A maturation function was applied to describe the clearance of remdesivir and GS-704277 in the youngest subjects.
Older participants (≥60 years) showed a lower central volume of distribution (32.4% decrease) of GS-704277 and a lower clearance (CL) (34.1% decrease) of GS-441524. Hospitalised COVID-19 patients, adult and paediatric, had a lower CL (28.1% decrease) of GS-704277. Since there were no data from non-hospitalised paediatric COVID-19 patients, it was assumed that the effect of hospitalisation was the same in both adult and paediatric patients. Within the paediatric population,

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baseline ferritin was associated with a 20.1% decrease in the clearance of GS-704277, whereas baseline bilirubin was found to have an impact on the clearance (25% decrease) of GS-441524. Interindividual variability for Phase 3 data was estimated separately, since the unexplained variability was higher in the phase 3 studies than in the Phase 1 and Phase 2/3 studies.
Sensitivity analyses revealed that body weight was the most influential covariate for remdesivir in paediatric subjects, whereas baseline ferritin and baseline bilirubin showed the biggest impact for GS-704277 and GS-441524 exposures, respectively. Overall, no dose adjustments are required based on any of the evaluated covariates including age, sex, race, study population, ethnicity, baseline AST, baseline ALT, baseline total bilirubin, baseline albumin, baseline eGFR, baseline ferritin, baseline C-reactive protein, and oxygen support status.

4.2 Dose finding and dose recommendation

No dose finding studies were performed. The doses used in study GS-US-540-5823 were based on a physiologically-based pharmacokinetic (PBPK) model developed to characterise the PK of remdesivir (RDV) and the primary circulating nucleoside metabolite, GS-441524, in adults (SimCYP v.17, Certara). The adult PBPK model was subsequently used to predict paediatric patient exposure, accounting for age-dependent changes in organ volume or size (liver and kidney), esterase expression, plasma protein binding, and organ blood flow. Simulations indicated that the doses used result in exposures of both RDV and GS-441524 at or below that which was previously observed to be well tolerated in healthy volunteers.

4.3 Efficacy

The efficacy of remdesivir in the treatment of COVID-19 in paediatric patients is extrapolated from efficacy outcomes in adult studies based on comparable exposures for remdesivir, GS-704277, and GS-441524 between adult and paediatric patients. This approach is justified as the infection is largely similar in adults and children, even though COVID-19 may occur less frequently in children and children usually only have disease of mild to moderate severity. Furthermore, remdesivir directly acts on the virus and this activity is not expected to be different between adults and children.

Supportive data on efficacy and safety in children were provided with studies GS-US-540-5823 in paediatric patients hospitalised and requiring medical care for COVID-19 and GS-US-540-9012 in non-hospitalised patients, including adolescents, at risk for progressing to severe COVID-19. The latter study was already submitted and assessed in a previous application and will therefore not be extensively discussed here.

Study GS-US-540-5823 was a Phase 2/3, single-arm, open-label study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of remdesivir in the treatment of COVID-19 in paediatric patients.
In total, 53 patients aged 28 days to <18 years with PCR-confirmed COVID-19 who were hospitalised and required medical care for COVID-19 were included:

Cohort 1	≥12 years to <18 years and weighing ≥40 kg	n=12
Cohort 2	≥28 days to <18 years and weighing ≥20 to <40 kg	n=12
Cohort 3	≥28 days to <18 years and weighing ≥12 to <20 kg	n=12
Cohort 4	≥28 days to <18 years and weighing ≥3 to <12 kg	n=12
Cohort 8	<12 years and weighing ≥40 kg	n=5

Patients in cohorts 1 and 8 (bodyweight ≥40 kg) received the approved adult flat dose (200 mg loading dose followed by 100 mg QD IV for up to 10 days). Patients in cohorts 2 to 4 received a body weight-based dose (5 mg/kg loading dose followed by 2.5 mg/kg QD IV for up to 10 days).
Overall, 68% of the participants received RDV for 5 days or less (median [Q1, Q3] of 5 [4, 8] days) during the study. Of the 53 enrolled participants, 40 (75.0%) discontinued the study drug, mainly because of hospital discharge and at the investigator's discretion. Reasons for discontinuation of the

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study drug were different for patients in cohort 1 compared to the other cohorts, with notably fewer discontinuations due to hospital discharge and more discontinuations at the investigator's discretion.

At baseline, 43.4% of the participants were male, with a slightly higher proportion of males (58.3%) in cohort 3. The median body mass index was 18.8 kg/m^2, with a notably higher median BMI in cohort 1 (33.8 kg/m^2) and cohort 8 (28.0 kg/m^2). The median (Q1, Q3) duration of symptoms prior to treatment was 5 (3, 7) days, the median (Q1, Q3) duration of hospitalisation prior to treatment was 1 (1, 3) days, and the median baseline viral load was 4.63 $\log_{10}$ copies/mL from nasal swabs (n=18), 6.37 $\log_{10}$ copies/mL from nasopharyngeal swabs (n=24), and 5.50 $\log_{10}$ copies/mL from endotracheal tube aspirates (n=9). There was great variability in the duration of hospitalisation in cohorts 1 and 4 (maximum 88 and 82 days, respectively), and in the duration of symptoms prior to treatment in cohort 1 (maximum 177 days). Overall, the majority of patients (57%) were on high-flow oxygen, i.e. had score 3 on the 7-point ordinal scale (34%) or invasive mechanical ventilation (IMV)/extracorporeal membrane oxygenation (ECMO), i.e. score 2 on the 7-point ordinal scale score (23%). Baseline disease severity based on the ordinal scale seems somewhat less severe for cohorts 3 and 8, i.e. in these cohorts a higher proportion of patients were on low-flow oxygen or were not given supplemental oxygen (Cohort 1: 41.7%, Cohort 2: 41.7%, Cohort 3: 50.0%, Cohort 4: 33.3%, Cohort 8: 60.0%).

The most common medical conditions were obesity (cohort 1: 58%, cohort 2: 17%, cohort 3: 27%, cohort 4: 27%, cohort 8: 80%), asthma (cohort 1 25%, cohort 2 42%, cohort 3 17%, cohort 4 0%, cohort 8 20%), and cardiac disorders (cohort 1: 17%, cohort 2: 25%, cohort 3: 17%, cohort 4: 33%, cohort 8: 0%). Differences in baseline characteristics are difficult to interpret due to the small number of patients in each cohort.

Efficacy was only evaluated as secondary endpoints and no formal statistical analyses were conducted. For all cohorts, improvement of clinical status on the 7-point ordinal scale over time was observed. However, improvement was mostly seen in those not on IMV or ECMO, which is in line with the currently approved indication.

For participants who were discharged alive by Day 30, the median (Q1, Q3) duration of hospitalisation from Day 1 was 7 (5, 12) days. The proportion of total participants who were discharged from the hospital alive was 60.4% by Day 10 and 83.0% by Day 30. Among the participants who were not discharged alive by Day 30, 7 were still hospitalised and 2 had died.

Overall, cohort 3 showed the most and fastest improvement, including hospital discharge, while cohort 1 showed the least and slowest improvement. However, due to the low number of patients in each cohort, results should be interpreted with caution.

The efficacy data are only descriptive, and due to the study design without a control arm, no conclusions can be drawn regarding the efficacy of remdesivir treatment in the paediatric population.

Study GS-US-540-9012 was a Phase 3, randomised, double-blind, placebo-controlled, multicentre study of RDV therapy for outpatients with early-stage COVID-19 who are at higher risk of disease progression. Patients were randomised to receive remdesivir 200 mg IV on Day 1 and 100 mg QD on subsequent days for a total of 3 days or placebo IV for 3 days.

None of the adolescent participants included in this study (8 participants ≥12 to <18 years; 3 received remdesivir, 5 received placebo) had a COVID-19 related hospitalisation, or MAV (medical visits attended by the participant and a health care professional) by Day 28 and none of the adolescent participants died during the study.

4.4 Safety

Safety data for the paediatric population are based on data from 53 participants aged ≥28 days to <18 years who received at least 1 dose of RDV in study GS-US-540-5823, as well as 3 participants aged ≥12 to <18 years who received at least 1 dose of RDV in study GS-US-540-9012.

In study GS-US-540-5823, participants received RDV for a median (Q1, Q3) of 5 (4, 8) days during the study (median of 5 days in each cohort).

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All 3 adolescent participants in study GS-US-540-9012 received RDV for the full 3-day treatment duration approved for patients who do not require supplemental oxygen or hospitalisation for COVID-19.

GS-US-540-5823

Overall summary of adverse events (safety analysis set)

	Cohort 1: 12 to < 18 Years and ≥ 40 kg (N = 12)	Cohort 2: 28 Days to < 18 Years and 20 to < 40 kg (N = 12)	Cohort 3: 28 Days to < 18 Years and 12 to < 20 kg (N = 12)	Cohort 4: 28 Days to < 18 Years and 3 to < 12 kg (N = 12)	Cohort 8: < 12 Years and ≥ 40 kg (N = 5)	Total (N = 53)
AE	11 (91.7%)	7 (58.3%)	9 (75.0%)	7 (58.3%)	4 (80.0%)	38 (71.7%)
Grade 3 or higher AE	6 (50.0%)	2 (16.7%)	1 (8.3%)	4 (33.3%)	2 (40.0%)	15 (28.3%)
Study drug-related AE	4 (33.3%)	1 (8.3%)	0	1 (8.3%)	2 (40.0%)	8 (15.1%)
Study drug-related Grade 3 or higher AE	3 (25.0%)	0	0	0	0	3 (5.7%)
SAE	5 (41.7%)	2 (16.7%)	0	3 (25.0%)	1 (20.0%)	11 (20.8%)
Study drug-related SAE	0	0	0	0	0	0
AE leading to premature study drug discontinuation	2 (16.7%)	0	0	0	0	2 (3.8%)
Treatment-emergent death	1 (8.3%)	1 (8.3%)	0	0	1 (20.0%)	3 (5.7%)

AE = adverse event; DAIDS = Division of AIDS; MedDRA = Medical Dictionary for Regulatory Activities
Adverse events were coded using MedDRA Version 24.0.
Severity grades were defined by the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, July 2017.
Treatment-emergent death refers to deaths that occurred between the first dose date and the last dose date plus 30 days (inclusive).
One participant died 32 days after the last dose date and is not counted as a treatment-emergent death.

The most common AEs were

- Cohort 1: acute kidney injury (4 participants, 33.3%), constipation (3 participants, 25.0%), ALT increased (2 participants, 16.7%), and hypertension (2 participants, 16.7%)
- Cohort 2: pyrexia, bradycardia, and infusion-site extravasation (2 participants, 16.7% each)
- Cohort 3: agitation (2 participants, 16.7% each)
- Cohort 4: hyperglycaemia (2 participants, 16.7% each)
- Cohort 8: constipation (3 participants, 60.0%) and hypomagnesaemia (2 participants, 40.0%)

The most common drug related AEs were ALT increased (n=3, 5.7%) and AST increased (n=2, 3.8%).

There were no reported SAEs considered as being related to the study drug.

Differences in safety between the cohorts were noted, with cohort 1 showing the least disease improvement and more frequent and more severe AEs compared to the other cohorts. Additional information was provided by the applicant in response to questions from the EMA addressing these issues, with special attention given to the high number of cases of acute kidney injury observed in cohort 1. In the EMA assessment it was concluded that the cases of acute kidney injury were not related to remdesivir treatment. Furthermore, there appeared to be no clear relation between exposure and efficacy or safety, and overall it was concluded that the differences observed between cohorts most likely reflect the small sample size and study design. This conclusion can be endorsed, although it is somewhat unsatisfactory that the observed differences could not be fully explained.

CO-US-540-9012

None of the adolescent participants in the RDV group experienced any AE during the study.

Overall, based on data from both studies, remdesivir treatment was tolerated well and no relevant new safety findings were noted in paediatric patients compared to the known safety profile in adults. However, the safety database is small. Furthermore, without a control group and with part of the

population having a complex underlying medical condition, the safety observations in study GS-US-540-5823 are difficult to interpret.

4.5 Final clinical benefit risk assessment

An extension of the indication for remdesivir in the treatment of COVID-19 to paediatric patients is requested.

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 benign to severe, with the majority having mild to moderate disease, including flu-like symptoms up to mild pneumonia. Some infected patients, however, develop severe to critical disease with complications including acute respiratory distress syndrome (ARDS), septic shock, and various end organ damage (e.g. kidney, heart).

Children more often have asymptomatic infection or mild disease, but can develop severe and critical disease as well. The risk of progressing to severe disease is increased in children with comorbidities. In Switzerland, there are currently no antiviral treatments approved for COVID-19 in children.

The efficacy and safety of remdesivir in the treatment of COVID-19 in paediatric patients are based on extrapolation of efficacy outcomes in studies in adults. In addition, in support of the application, data on efficacy and safety from studies GS-US-540-5823 in paediatric patients who were hospitalised and requiring medical care for COVID-19 and GS-US-540-9012 in non-hospitalised patients, including adolescents, at risk for progressing to severe COVID-19 were submitted. Risk factors for disease progression in adolescent participants in study GS-US-540-9012 were chronic lung disease, diabetes mellitus, and obesity.

Beneficial effects and any associated uncertainties

Following the administration of remdesivir at the requested doses, remdesivir and GS-704277 were increased by up to approximately two-fold in paediatric patients compared to adult exposures, whereas GS-441524 exposures were comparable. However, the variability, particularly in the adult data, was generally significant, and the paediatric exposures were overall within the range of exposures observed in adults.

In study GS-US-540-5823, improvement of clinical status based on the 7-point ordinal scale over time was shown, mainly for cohorts 2, 3, 4 and 8. The improvement was mainly seen for those who were not on IMV or ECMO. Furthermore, the proportion of total participants who were discharged from the hospital alive was 60.4% by Day 10 and 83.0% by Day 30. Among the participants who were not discharged alive by Day 30, 7 were still hospitalised and 2 had died. For participants who were discharged alive by Day 30, the median (Q1, Q3) duration of hospitalisation from Day 1 was 7 (5, 12) days.

In study GS-US-540-9012, none of the 8 adolescents (3 remdesivir, 5 placebo) included had a COVID-19 related hospitalisation or medical attended visit by Day 28 and none died during the study.

Due to the limited data from study GS-US-540-9012 and the study design without a control group and formal statistical testing of efficacy endpoints in study GS-US-540-5823, these data do not allow conclusions regarding the efficacy of remdesivir in paediatric patients, and can only be considered supportive.

Differences in efficacy and safety between the cohorts were noted, with cohort 1 showing the least improvement and more frequent and more severe AEs compared to the other cohorts. Additional information was provided by the applicant in response to questions from the EMA addressing these issues. There appeared to be no clear relationship between exposure and efficacy or safety, and overall it was concluded that the differences observed between cohorts most likely reflect the small sample size and study design. This conclusion can be endorsed, although it is somewhat unsatisfactory that the observed differences could not be fully explained.

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Unfavourable effects and any associated uncertainties

Safety data for the paediatric population are based on data from 53 participants aged ≥28 days to <18 years from study GS-US-540-5823, as well as 3 participants aged ≥12 to <18 years from study GS-US-540-9012.

Overall, remdesivir treatment was tolerated well and no relevant new safety findings were noted in paediatric patients compared to the known safety profile in adults. However, the safety database is small and the data do not allow firm conclusions regarding the safety profile.

Special attention was given to the high number of cases of acute kidney injury observed in cohort 1, but based on additional information provided by the applicant in response to questions from the EMA it was concluded that these cases were not related to remdesivir treatment.

Overall, the provided data indicate similar exposures for remdesivir and its metabolites GS-704277 and GS-441524 following administration of remdesivir at the doses requested in paediatric patients compared to adult patients. The efficacy of remdesivir in the treatment of COVID-19 in paediatric patients can therefore be assumed based on efficacy demonstrated in adult patients. The provided data on efficacy and safety in paediatric patients can only be considered supportive due to small sample size and other limitations in study design. In particular, in the study GS-US-540-5823 the lack of a control group renders the efficacy and safety outcomes difficult to interpret. Given the medical need, as there are currently no treatments approved for children under 12 years of age, the uncertainties regarding the submitted efficacy and safety data can be accepted.

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5 Risk management plan summary

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

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6 Appendix

Approved information for healthcare professionals

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

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

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

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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®

Composition

Veklury 100 mg powder for concentrate for solution for infusion

Active substances

Remdesivir

Excipients

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

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

Pharmaceutical form and active substance quantity per unit

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

Indications/Uses

Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in

- adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment),
- adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen or hospitalisation for COVID-19 and who are at increased risk of developing a severe COVID-19 course

(see “Properties/Effects”).

Dosage/Administration

Veklury should be used under conditions where treatment of severe hypersensitivity reactions, including anaphylaxis, is possible. Patients should be monitored when receiving Veklury (see section “Warnings and precautions”).
Treatment should be intiated as soon as possible after a positive viral test for SARS-CoV-2 (see “Properties/Effects”).

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

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

Table 2: Treatment duration

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

Special dosage instructions

Patients with impaired hepatic function

The pharmacokinetics of remdesivir 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 remdesivir 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 remdesivir is required in patients over the age of 65 years (see “Properties/Effect” and “Pharmacokinetics”).

Paediatric patients

The safety and efficacy of remdesivir in children children less than 4 weeks of age and weighing less than 3 kg have not yet been established. No data are available.

Mode of administration

For intravenous infusion use.

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

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

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

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

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

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

Infusion Bag Volume	Infusion Time	Rate of Infusion[a]
100 ml	30 min	3.33 ml/min
	60 min	1.67 ml/min
	120 min	0.83 ml/min
50 ml	30 min	1.67 ml/min
	60 min	0.83 ml/min
	120 min	0.42 ml/min
25 ml	30 min	0.83 ml/min
	60 min	0.42 ml/min
	120 min	0.21 ml/min

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

Contraindications

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

Warnings and precautions

Hypersensitivity including infusion-related and anaphylactic reactions

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

Transaminase elevations

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

- Remdesivir should not be initiated in patients with alanine aminotransferase (ALT) ≥ 5 times the upper limit of normal (ULN) at baseline
- Remdesivir should be discontinued in patients who develop:
  - ALT ≥ 5 times the ULN during treatment with remdesivir. 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 remdesivir and while receiving it as clinically appropriate. Remdesivir 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 remdesivir and chloroquine phosphate or hydroxychloroquine sulphate is not recommended based on cell culture data demonstrating an antagonistic effect of chloroquine on the

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

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.

Interactions

No clinical interaction studies have been performed with remdesivir. The overall potential for interactions is currently unknown; patients should remain under close observation during the days of remdesivir administration. Due to antagonism observed in cell culture, concomitant use of remdesivir 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, 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 OAT3, OCT1, MATE-1, OATP1B1 and OATP1B3 *in vitro*. No inhibition potencial predicted for OAT1 and OCT2.

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 remdesivir 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 UGT, 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 P-gp 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 enzyme CYP3A4, and is a substrate for Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and P-glycoprotein (P-gp) transporters.

The potential of interaction of remdesivir with inhibitors/inducers of the hydrolytic pathway (esterase) or CYP3A4 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 remdesivir as remdesivir 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 or limited amount of data from the use of remdesivir in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see “Preclinical Data”). Remdesivir 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 remdesivir 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 remdesivir on fertility are available. In male rats, there was no effect on mating or fertility with remdesivir treatment. In female rats, however, an impairment of fertility was observed (see “Preclinical data”). The relevance for humans is unknown.

Effects on ability to drive and use machines

No corresponding studies have been performed.

Undesirable effects

Summary of the safety profile

The safety profile of Veklury is based on data from 4 Phase 1 studies in healthy adults, 3 Phase 3 studies in hospitalised patients with COVID-19, 1 Phase 3 study in non-hospitalised patients with COVID-19, from hospitalised patients with COVID-19 who received Veklury in a compassionate use program and from post-marketing experience. The most common adverse reaction in healthy 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 5 are listed below by system organ class and frequency. Frequencies are defined as follows: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), not known (frequency cannot be estimated from the available data).

Table 5: Tabulated list of adverse reactions

Frequency	Adverse reaction
Immune system disorders	
Rare	hypersensitivity
Not known	anaphylactic reaction[1]
Nervous system disorders	
Common	headache
Cardiac disorders	
Not known	sinus bradycardia[2]
Gastrointestinal disorders	
Common	nausea
Hepatobiliary disorders	
Very common	transaminases increased (14%)
Skin and subcutaneous tissue disorders	
Common	rash
Investigations	
Very common	prothrombin time prolonged (44%)
Injury, poisoning and procedural complications	
Rare	infusion-related reaction

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

Description of selected undesirable effects

Transaminases Increased

In healthy volunteer studies, increases in ALT, aspartate aminotransferase (AST) or both in subjects who received remdesivir 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), any grade (≥ 1.25 × upper limit of normal (ULN)) laboratory abnormalities of increased AST and increased ALT occurred in 33% and 32% of patients, respectively, receiving remdesivir compared with 44% and 43% of patients, respectively, receiving placebo. Grade ≥ 3 (≥ 5.0 × ULN) laboratory abnormalities of increased AST and increased ALT occurred in 6% and 3% of patients, respectively, receiving remdesivir compared with 8% and 6% of patients, respectively, receiving placebo. In a randomised, open-label multi-centre clinical study (Study GS-US-540-5773) in hospitalised patients with severe COVID-19 receiving remdesivir for 5 (n=200) or 10 days (n=197), any grade laboratory abnormalities of increased AST and increased ALT occurred in 40% and 42% of patients, respectively, receiving remdesivir. Grade ≥ 3 laboratory abnormalities of increased AST and increased ALT both occurred in 7% of patients receiving remdesivir. In a randomised, open-label multi-centre clinical study (Study GS-US-540-5774) in hospitalised patients with moderate COVID-19 receiving remdesivir 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 remdesivir, 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 remdesivir and 6% and 8%, respectively, receiving standard of care.

Prothrombin time increased

In a clinical study (NIAID ACTT-1) of patients with COVID-19, the incidence of increased prothrombin time or INR (predominantly Grades 1-2) was higher in subjects who received remdesivir compared to placebo, with no difference observed in the incidence of bleeding events between the two groups. Prothrombin time should be monitored while receiving remdesivir as clinically appropriate. In Study GS-US-540-9012, the incidence of increased prothrombin time or INR was similar in patients treated with remdesivir compared to placebo.

Paediatric population

The safety assessment of remdesivir in children 4 weeks of age and older and weighing at least 3 kg with COVID-19 is based on data from a Phase 2/3, open-label clinical study (Study GS-US-540-5823) that enrolled 53 patients who were treated with remdesivir. The adverse reactions observed were consistent with those observed in clinical trials of remdesivir in adults. Additionally, isolated cases of upper abdominal pain, constipation, hemoglobin decreased, and hyperbilirubinaemia were observed as adverse reactions in GS-US-540-5823.

Reporting of suspected undesirable effects

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

Overdose

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

Properties/Effects

ATC code

J05AB16

Mechanism of action

Remdesivir is an adenosine nucleotide prodrug that is metabolised within host cells to form the pharmacologically active nucleoside triphosphate metabolite. Remdesivir triphosphate acts as an analog of adenosine triphosphate (ATP) and competes with the natural ATP substrate for incorporation into nascent RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase, which results in delayed chain termination during replication of the viral RNA. As an additional mechanism, remdesivir triphosphate can also inhibit viral RNA synthesis following its incorporation into the template viral RNA as a result of read-through by the viral polymerase that may occur in the presence of higher nucleotide concentrations. When remdesivir nucleotide is present in the viral RNA template, the efficiency of incorporation of the complementary natural nucleotide is compromised, thereby inhibiting viral RNA synthesis.

Pharmacodynamics

Antiviral Activity

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

The antiviral activity of remdesivir was antagonised by chloroquine phosphate in a dose-dependent manner when the two drugs were co-incubated at clinically relevant concentrations in HEp-2 cells

infected with respiratory syncytial virus (RSV). Higher remdesivir EC_{50} values were observed with increasing concentrations of chloroquine phosphate. Increasing concentrations of chloroquine phosphate reduced formation of remdesivir triphosphate in A 549-hACE2, HEp-2 and normal human bronchial epithelial cells.

Based on in vitro testing, remdesivir retained similar antiviral activity (<2.5-fold change) against clinical isolates of SARS-CoV-2 variants containing the P323L substitution in the viral polymerase including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Epsilon (B.1.429), Zeta (P.2), Iota (B.1.526), Kappa (B.1.617.1), Lambda (C.37) and Omicron (B.1.1.529 sub-lineages BA.1, BA.2, BA.2.12.1, BA.4, BA.5) variants compared to earlier lineage SARS-CoV-2 (lineage A) isolates. The antiviral activity of remdesivir against SARS-CoV-2 variants is presented in Table 6.

Table 6: Remdesivir Antiviral Activity Against Clinical Isolates of SARS-CoV-2 Variants

SARS-CoV-2 Lineage	**WHO Nomenclature**	**Key Substitutions**	**Remdesivir EC_{50} (nM) Replicates (n)**	**Fold Change in Susceptibility[a,b]**
B.1.1.7	Alpha	P323L	192 (6)	1.58
B.1.351	Beta	P323L	141 (6)	1.19
P.1	Gamma	P323L	97 (6)	0.82
B.1.617.2	Delta	P323L, G671S	70 (13)	0.59
B.1.429	Epsilon	P323L	210 (8)	1.94
P.2	Zeta	P323L	151 (5)	1.17
B.1.526	Iota	P323L	258 (8)	2.33
B.1.617.1	Kappa	P323L	77 (6)	0.63
C.37	Lambda	P323L	175 (6)	1.37
B.1.1.529	Omicron			
BA.1		P323L	44 (6)	0,45
BA.2		P323L	25 (2)	0,23
BA.2.12.1		P323L	33 (2)	0,20
BA.4		P323L	25 (2)	0,15
BA.5		P323L	106 (2)	0,66

a The fold change relative to the lineage A SARS-CoV-2 reference strain (WA1) included in each experiment was calculated for each variant.
b Fold-change: <2.5 is not significant based on assay variability. All variants show no reduction in susceptibility.

Resistance

In Cell Culture

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

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

In Clinical Trials

In NIAID ACTT-1 Study (see “Clinical Efficacy”), among 61 patients with baseline and post-baseline sequencing data available, the rate of emerging substitutions in the viral RNA-dependent RNA polymerase was similar in patients treated with remdesivir compared to placebo. In 2 patients treated with remdesivir, substitutions in the RNA-dependent RNA polymerase previously identified in resistance selection experiments (V792I or C799F) and associated with low fold change in remdesivir susceptibility (≤3.4-fold) were observed. No other RNA-dependent RNA polymerase substitutions observed in patients treated with remdesivir were associated with resistance to remdesivir.

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

Clinical efficacy

Clinical Studies in Subjects with COVID-19

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

A randomised, double-blind, placebo-controlled clinical study evaluated remdesivir 200 mg once daily for 1 day followed by remdesivir 100 mg once daily for up to 9 days (for a total of up to 10 days of intravenously administered therapy) in hospitalised adult patients with COVID-19 with evidence of lower respiratory tract involvement. The study enrolled 1062 hospitalised patients: 105 (9.9%) patients with mild/moderate disease (10% in both treatment groups) and 957 (90.1%) patients with severe disease (90% in both treatment groups). Mild/moderate disease was defined as SpO2 > 94% and respiratory rate < 24 breaths/minute without supplemental oxygen; severe disease was defined as an SpO2 ≤ 94% on room air, a respiratory rate ≥ 24 breaths/min, an oxygen requirement, or a requirement for mechanical ventilation. A total of 285 patients (26.8%) (n=131 received remdesivir) were on mechanical ventilation/Extracorporeal Membrane Oxygenation (ECMO). Patients were randomised 1:1, stratified by disease severity at enrolment, to receive remdesivir (n=541) or placebo (n=521), plus standard of care.

The baseline mean age was 59 years and 36% of patients were aged 65 or older. Sixty-four percent were male, 53% were White, 21% were Black, 13% were Asian. The most common comorbidities were hypertension (51%), obesity (45%), type 2 diabetes mellitus (31%); the distribution of comorbidities was similar between the two treatment groups.

Approximately 38.4% (208/541) of the patients received a 10-day treatment course with remdesivir.

The primary clinical endpoint was time to recovery within 29 days after randomisation, defined as either discharged from hospital (with or without limitations of activity and with or without home oxygen requirements) or hospitalised but not requiring supplemental oxygen and no longer requiring ongoing medical care. The median time to recovery was 10 days in the remdesivir group compared to 15 days in the placebo group (recovery rate ratio 1.29; [95% CI 1.12 to 1.49], p < 0.001).
The outcome differed relevantly between the two strata. In the severe disease stratum time to recovery was 11 days in the remdesivir group and 18 days in the placebo group (recovery rate ratio 1.31 [95% CI 1.12 to 1.52]). For the mild/moderate disease stratum, time to recovery was not different between the two groups (5 days for both, remdesivir and placebo).

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

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

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

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

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

Overall, after adjusting for between-group differences at baseline, patients receiving a 5-day course of remdesivir had similar clinical status at Day 14 as those receiving a 10-day course (odds ratio for improvement: 0.75; [95% CI 0.51 to 1.12]). In addition, there were no statistically significant differences in recovery rates or mortality rates in the 5-day and 10-day groups once adjusted for between group differences at baseline. All-cause 28-day mortality was 12% vs 14% in the 5- and 10-day treatment groups, respectively.

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

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

At baseline, the median age of patients was 57 years (range, 12 to 95 years); 61% were male, 61% were White, 19% were Black, and 19% were Asian. Baseline clinical status, oxygen support status,

and median duration of symptoms and hospitalization prior to first dose of remdesivir were similar across treatment groups.

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

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

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

Patients were randomized in a 1:1 manner, stratified by residence in a skilled nursing facility (yes/no), age (< 60 vs ≥ 60 years), and region (US vs ex-US) to receive remdesivir (n=279) or placebo (n=283), plus standard of care.

At baseline, mean age was 50 years (with 30% of patients aged 60 or older); 52% were male, 80% were White, 8% were Black, 2% were Asian, 44% were Hispanic or Latino; median body mass index was 30.7 kg/m^2. The most common comorbidities were diabetes mellitus (62%), obesity (56%), and hypertension (48%). Median (Q1, Q3) duration of symptoms prior to treatment was 5 (3, 6) days; median viral load was 6.3 log_{10} copies/ml at baseline. The baseline demographics and disease characteristics were well balanced across the remdesivir and placebo treatment groups. Post-hoc exploratory analysis of optional biomarker samples showed 14.8% of patients were serological positive at baseline and 37.7% were serological negative (47.5% did not consent to optional biomarker collection).

The primary endpoint was the proportion of patients with COVID-19 related hospitalisation (defined as at least 24 hours of acute care) or all-cause 28-day mortality. Events (COVID-19-related hospitalisation or all-cause 28-day mortality) occurred in 2 (0.7%) patients treated with remdesivir compared to 15 (5.3%) patients concurrently randomized to placebo, demonstrating an 87% reduction

in COVID-19-related hospitalisation or all-cause mortality compared to placebo (hazard ratio, 0.134 [95% CI, 0.031 to 0.586]; p=0.0076). No deaths were observed at Day 28. Six of the 17 hospitalisation events occurred in participants with known baseline serostatus (serological positive: n=0 in remdesivir group and n=2 in placebo group; serological negative: n=2 in remdesivir group and n=2 in placebo group). Eleven of the 17 hospitalisation events occurred in participants with unknown baseline serostatus in placebo group and none in the remdesivir group. No conclusion can be made on efficacy in the subgroups stratified by serostatus due to the small number of patients with known serostatus and overall low event rates.

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.

Paediatric population

The use of remdesivir in children is supported by results from studies conducted in adults and an open-label study (Study 5823) in 53 hospitalized pediatric patients (see "Pharmacokinetics, Pediatric and Adolescent Section").
Study GS-US-540-5823 is a single-arm, open-label study where the pharmacokinetics and safety of remdesivir in paediatric patients at least 28 days of age and weighing at least 3 kg with COVID-19 (n=53) was assessed. Efficacy endpoints were secondary and descriptively analysed and therefore these should be interpreted with caution. The study is ongoing.

Five cohorts were enrolled: patients ≥ 12 years and weighing ≥ 40 kg (n=12); patients < 12 years and weighing ≥ 40 kg (n=5); patients ≥ 28 days and weighing ≥ 20 to <40 kg (n=12); patients ≥ 28 days and weighing ≥ 12 to < 20 kg (n=12); and patients ≥ 28 days and weighing ≥ 3 to < 12 kg (n=12).

Patients weighing ≥ 40 kg received 200 mg of remdesivir on Day 1 followed by remdesivir 100 mg once daily on subsequent days; patients weighing ≥ 3 kg to < 40 kg received remdesivir 5 mg/kg on Day 1 followed by remdesivir 2.5 mg/kg once daily on subsequent days. A total of 13 patients (24.5%) received remdesivir for 10 days.

At baseline, median age was 7 years (Q1, Q3: 2 years, 12 years); 57% were female, 70% were White, 30% were Black, and 44% were Hispanic or Latino; median weight was 24.6 kg (range: 4 kg to 192 kg). A total of 19 patients (37%) were obese (BMI-for-age ≥ 95th percentile); 7 (58%), 2 (17%), 3 (27%), 3 (27%), and 4 (80%) patients in Cohorts 1, 2, 3, 4 and 8 respectively. The most common comorbidities were asthma (28%) and cardiac disorders (21%). A total of 12 patients (23%) were on invasive mechanical ventilation, 18 (34%) were on non-invasive ventilation or high-flow oxygen; 10 (19%) were on low-flow oxygen; and 13 (25%) were on room air, at baseline. The overall median (Q1,

Q3) duration of symptoms and hospitalization prior to first dose of remdesivir was 5 (3, 7) days and 1 (1, 3) day, respectively.

Overall median (Q1, Q3) change from baseline in clinical status (assessed on a 7-point ordinal scale ranging from death [score of 1] to ventilatory support and decreasing levels of oxygen to hospital discharge [score of 7]) was +2.0 (1.0, 4.0) points on Day 10.

Recovery (defined as an improvement from a baseline clinical status score of 2 through 5 to a score of 6 or 7, or an improvement from a baseline score of 6 to a score of 7) was reported for 62% of patients on Day 10; median (Q1, Q3) time to recovery was 7 (5, 16) days.

Overall, 60% of patients were discharged by Day 10. Most patients 92% (49/53) received at least 1 concomitant medication other than remdesivir for the treatment of COVID-19 including immune modulators and anti-inflammatory agents. Three patients died during the study.

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 remdesivir adult dosage regimen, peak plasma concentration was observed at end of infusion, regardless of dose level, and declined rapidly thereafter with a half-life of approximately 1 hour. Peak plasma concentrations of GS-441524 were observed at 1.5 to 2.0 hours post start of a 30 minute infusion.

Distribution

Remdesivir is approximately 88 to 93% bound to human plasma proteins (ex-vivo data). The binding is independent of drug concentration over the range of 1 to 10 µM, with no evidence for saturation of remdesivir binding. Protein binding of GS-441524 was low (2% bound) in human plasma. After a single 150 mg dose of [^{14}C]-remdesivir in healthy 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 initial hydrolysis to an intermediate metabolite, GS-704277. This reaction is catalyzed primarily (80%) by CES1 enzymes,

with minor contributions from cathepsin A and CYP3A (approximately 10% each). Phosphoramidate cleavage of GS-704277, catalyzed by the enzyme HINT1, is then followed by successive phosphorylation to form the active triphosphate, GS-443902. Dephosphorylation of all phosphorylated metabolites can result in the formation of nucleoside metabolite GS-441524 that itself is not efficiently re-phosphorylated. Decyanation of remdesivir and/or its metabolites, followed by subsequent rhodanese mediated conversion generates thiocyanate anion. The levels of thiocyanate detected following administration of 100 mg and 200 mg remdesivir were observed to be significantly below endogenous levels in human plasma.

Elimination

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

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 have 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 have 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. Remdesivir should not be used in patients with eGFR < 30 ml/min.

Paediatric patients

Population pharmacokinetic models for remdesivir and its circulating metabolites (GS-704277 and GS-441524), developed using pooled data from studies in healthy adults and in adult and paediatric patients with COVID-19, were used to predict pharmacokinetic exposures in 50 paediatric patients aged ≥ 28 days to < 18 years and weighing ≥ 3 kg (Study GS-US-540-5823). Geometric mean exposures (AUC_{tau} and C_{max}) of remdesivir (44% to 147%), GS-704277 (-21% to 25%), and GS-

441524 (7% to 91%) predicted for these patients at the doses administered were higher as compared to those in adult patients with COVID-19; however, the increases were not considered clinically significant.

Table 7: Pharmacokinetic parameters[a] estimate of steady-state plasma remdesivir, GS-441524 and GS-704277 in paediatric and adult hospitalised COVID-19 patients

Parameters Mean[b]	Paediatric patients					Adult hospitalised patients (N=277)
	Cohort 1	Cohort 8	Cohort 2	Cohort 3	Cohort 4	
	12 to <18 years and weighing ≥40 kg (N=12)	<12 years and weighing ≥40 kg (N=5)	28 days to <18 years and weighing 20 to <40 kg (N=12)	28 days to <18 years and weighing 12 to <20 kg (N=11)	28 days to <18 years and weighing 3 to <12 kg (N=10)	
Remdesivir						
C_{max} (ng/mL)	3910	3920	5680	5530	4900	2650
AUC_{tau} (h•ng/mL)	2470	2280	3500	3910	2930	1590
GS-441524						
C_{max} (ng/mL)	197	162	181	158	202	170
AUC_{tau} (h•ng/mL)	3460	2640	2870	2400	2770	3060
C_{tau} (ng/mL)	98.3	76.2	73.8	69.4	78.4	78.4
GS-704277						
C_{max} (ng/mL)	307	278	423	444	390	233
AUC_{tau} (h•ng/mL)	815	537	754	734	691	501

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

Preclinical data

Toxicology

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

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.

Other information

Incompatibilities

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

Shelf life

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

Shelf life after opening

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

Special precautions for storage

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

Instructions for handling

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

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

Preparation of Veklury solution for infusion
Reconstitution
Remove the required number of single-use vial(s) from storage. For each vial:

- Aseptically reconstitute remdesivir powder for concentrate for solution for infusion by addition of 19 ml of sterile water for injections using a suitably sized syringe and needle per vial.
  - Discard the vial if a vacuum does not pull the sterile water for injections into the vial.
- Only use **sterile water** for injection to reconstitute Veklury.
- Immediately shake the vial for 30 seconds.
- Allow the contents of the vial to settle for 2 to 3 minutes. A clear solution should result.
- If the contents of the vial are not completely dissolved, shake the vial again for 30 seconds and allow the contents to settle for 2 to 3 minutes. Repeat this procedure as necessary until the contents of the vial are completely dissolved.
- Inspect the vial to ensure the container closure is free from defects and the solution is free of particulate matter.
- Dilute immediately after reconstitution.

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

Adults and paediatric patients (weighing at least 40 kg)

- Using Table 8, determine the volume of sodium chloride 9 mg/ml (0.9%) solution for injection to withdraw from the infusion bag.

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

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

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

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

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

Authorisation number

68026 (Swissmedic)

Packs

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

Marketing authorisation holder

Gilead Sciences Switzerland Sàrl, Zug

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