swissmedic

Date: 18 October 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 24 May 2022

Note:

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

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

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
COVID-19	Coronavirus disease 2019
CYP	Cytochrome P450
DDI	Drug-drug interaction
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
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
IV	Intravenous
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
PS	Propensity score
PSP	Pediatric study plan (US FDA)
RDV	Remdesivir
RMP	Risk management plan
RRR	Recovery rate ratio
RSS	Risk-set sampling
RSV	Respiratory syncytial virus
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOC	Standard of care
SpO_2	Oxygen saturation
SwissPAR	Swiss Public Assessment Report

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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)
VOC	Variant of concern

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2 Background information on the procedure

2.1 Applicant's request(s)

OPEN project EMA
Swissmedic has been participating in the EMA's OPEN project. Further information at*: EMA COVID-19 assessments 'OPEN' to non-EU regulators | European Medicines Agency (europa.eu)*

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** (*new*)

Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19):
- in adults with pneumonia requiring supplemental oxygen,
- *in adults with pneumonia not requiring supplemental oxygen.*

(See "Properties/Effects".)

2.2.2 Approved indication

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

2.2.3 Requested dosage

The posology remains identical to the currently approved posology.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	12 January 2021
Formal control completed	14 January 2021
List of Questions (LoQ)	12 April 2021
Response to LoQ	1 July 2021
Preliminary decision	17 September 2021
Response to preliminary decision	16 November 2021
2nd Preliminary decision	3 March 2022
Response to 2nd preliminary decision	30 March 2022
Final decision	24 May 2022
Decision	approval

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3 Medical context

Coronavirus disease 2019 (COVID-19) is 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.

A number of 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 are a result of a hyperinflammatory response. 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 type 2 diabetes mellitus.

Vaccines based on various technologies have been developed for the prevention of COVID-19 and are widely used in Switzerland. Current available therapeutics depending on the state of the disease and patients' characteristics are essentially dexamethasone, remdesivir, and baricitinib+remdesivir. For treatment of non-hospitalised patients, several monoclonal antibodies were approved in Switzerland at the time of the assessment of the application. Of note, since the efficacy of monoclonal antibodies depend on their ability to bind to the spike protein, their efficacy can be reduced against some variants of concern (VOCs). Therefore, there remains a need for effective treatment options for non-hospitalised patients.

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4 Clinical aspects

4.1 Clinical pharmacology

The clinical pharmacology of Veklury was assessed as part of the initial application. No new clinical pharmacology data were submitted for the current application.

4.2 Dose finding and dose recommendation

Dose finding was assessed as part of the initial application. No adjustments to the approved dose recommendations were initially proposed in the current application to extend the indication.

In response to issues raised in the preliminary decision, the Applicant proposed a treatment duration of 3 days for the treatment of COVID-19 in non-hospitalised patients who do not require supplemental oxygen. This is a substantially shorter treatment duration than currently approved and evaluated in the studies in hospitalised patients. No clear justification is given for this shorter treatment duration. Although the optimal treatment duration remains unclear, the treatment duration of 3 days applied for can be accepted based on the outcome of Study GS-US-540-9012.

4.3 Efficacy

In the assessment of the data, the available assessment reports and respective product information from EMA and FDA were also taken into account.

Study **GS-US-540-5774** was a randomised, open-label, multicentre study to evaluate the efficacy of two remdesivir regimens with respect to clinical status in participants with moderate COVID-19. The study consisted of two parts: Part A, comparing two different treatment durations and standard of care, and Part B, a single group study of remdesivir in participants with moderate COVID-19.

The primary endpoint was clinical status assessed by a 7-point ordinal scale on Day 11 in line with the recommendations in the FDA guideline. However, the observed distribution over the whole ordinal scale results is difficult to interpret. Besides that, the endpoint is subjective as determining the score on the ordinal scale involves investigators' individual assessment of patients' clinical status and may also be influenced by hospitals' procedures for management and discharge of these patients. Together with the open-label design, this may introduce bias and have an influence on the study results.

The study populations were hospitalised patients 18 years of age, or aged ≥12 and <18 years of age weighing ≥40 kg with laboratory-confirmed SARS-CoV-2 infection, SpO_2 >94% on room air, and with radiographic infiltrates by imaging study. Patients who required mechanical ventilation at screening or patients with evidence of multiorgan failure were excluded. Patients with impaired liver function (ALT or AST > 5 times the upper limit of normal), or renal impairment (eGFR <50 ml/min) were excluded.

Subjects were randomised in a 1:1:1 ratio to receive continued standard of care therapy only, or 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.

Results

Of 612 subjects who were screened, 596 were randomised, and 384 received at least 1 dose of study treatment; 5-day treatment n=191, 10-day treatment n=193, and SOC n=200. More patients prematurely discontinued the study drug in the 10-day treatment group (5-day treatment group 24.1%; 10-day treatment group 62.2%), mainly because of discharge from the hospital.

The mean (SD) age of patients was 56.0 (15.1) years. Slightly more patients ≥75 years of age (with older age being an important prognostic factor for severe course of disease) 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 days (5, 11) 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. Although eligible patients were hospitalised patients requiring medical care, several patients had a baseline ordinal score 6 (hospitalised, not requiring supplemental oxygen, no longer requiring medical care).

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 seem to be worse than in the 5-day treatment group. After assessment of the responses to LoQ, the reasons for this difference remain unclear and the clinical relevance is unknown.

Given the open-label design and the relatively subjective endpoint, this study cannot be considered confirmatory and conclusions regarding better efficacy of remdesivir over SOC and optimal treatment duration should be made with caution. In addition, as only 37.8% of subjects 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-day treatment duration. This further complicates the interpretation of the finding that 5-day treatment duration seems to be more beneficial than 10 days.

At 11 days, there were no deaths in the 5-day treatment group versus 2 (1%) in the 10-day treatment group and 4 (2%) in the SOC group. However, deaths also occurred after day 11.

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 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, 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

In the subgroup of patients with mild to moderate disease, 82 received remdesivir and 76 received placebo. At the time of the analysis, less than half of the patients in each treatment group received the planned full 10-day treatment course and the results may therefore not be fully representative of a 10-day treatment duration.

The mean age of patients was 58.9 years, with 36% aged >65 years, and 64% were male. Overall, 53% of the patients were white, 21% were black. Median time (IQR) from symptom onset to randomisation was 9 (6-12) days and comparable between treatment arms. 159 (15%) patients had mild to moderate disease.

Overall, patients in the remdesivir group had a shorter time to recovery than patients in the placebo group (median, 10 days, as compared with 15 days; rate ratio for recovery 1.29 [1.12 to 1.49]; P<0.001). In participants in the mild-to-moderate disease stratum at randomisation, the median time to recovery was numerically shorter in the remdesivir 10-day group (5 days) than in the placebo group (7 days) (RRR 1.10; 95% CI: 0.80, 1.53). This primary endpoint was in line with the recommendations in the FDA guideline, although there is currently no single recommended endpoint for the evaluation of efficacy in the treatment of COVID-19. It was also different from the primary endpoint in study GS-US-540-5774 in patients with mild to moderate disease, complicating comparability.

Although the primary outcome did not substantially differ when adjusted for baseline ordinal score, a statistically significant benefit of remdesivir over placebo in rate ratio of recovery was seen only in patients with baseline category 5 score (receiving oxygen), and not for patients without supplemental 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.

A secondary analysis of data from CO-US-540-5776 presented in the Applicant's response to LoQ showed a numerical, but not statistically significant, benefit of remdesivir over placebo in the rate of clinical deterioration. In addition, it was estimated that days of ICU therapy were saved for the patients on room air at baseline. However, these findings are based on analysis of additional endpoints and were at this time only described in a manuscript. No reliable conclusions can therefore be based on these outcomes.

The applicant's reasoning that for the endpoint "improvement of clinical status" the results from the Day 15 comparison between the remdesivir 10-day group and the placebo group for the participants on room air were similar to those of the Study GS-US-540-5774. Day 14 comparison between the remdesivir groups and the SOC group is not agreed. Such a cross-study comparison is not possible due to the differences in study design, timing of the assessment of the endpoint, treatment duration, etc. Furthermore, the presented outcomes at Day 14 result from subgroup analysis (CO-US-540-5776) and secondary endpoints (GS-US-540-5774) not controlled for multiplicity. Further uncertainties on the outcomes of study GS-US-540-5774 result from the proportional odds assumption for the analysis not being met.

In conclusion, the results of CO-US-540-5776 cannot fully confirm the findings of GS-US-540-5774.

The applicant submitted real world data evaluating the effectiveness of remdesivir treatment in hospitalised patients with COVID-19. The primary outcome was all-cause mortality, different to the primary endpoint used in studies GS-US-540-5774 and CO-US-540-5776, limiting comparability.

The data source for this analysis was HealthVerity, a database containing hospital chargemaster data (transactional data for inpatient and outpatient encounters) and medical and pharmacy claims data from the US. Included were adult hospitalised COVID-19 patients from which remdesivir-exposed and matched referent patients were selected using a risk-set sampling (RSS) approach. The analysis was based on propensity score (PS)-balanced sets (1:1 PS matching) of the RSS nested cohort.

The analysis included 15,709 remdesivir-exposed and 15,709 matched control patients who were not receiving supplemental oxygen. Overall, the presented results for the hospital discharge were inconclusive. Remdesivir was associated with both a statistically significantly 1) reduced all-cause mortality and 2) increased likelihood of hospital discharge by day 28 after 5 days of remdesivir treatment. Overall, treatment effects were relatively small and the study might have been overpowered. In a sensitivity analysis, there was evidence of a longer time to discharge associated with remdesivir, contradictory to the primary analysis of the secondary endpoint.

In response to the above uncertainties regarding studies GS-US-540-5774 and CO-US-540-5776 and the effectiveness data that were raised in the preliminary decision, the Applicant submitted data of an additional study: **GS-US-540-9012**—a phase 3, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of remdesivir in the treatment of COVID-19 in an outpatient setting.

In this study, 562 adult patients with confirmed COVID-19 and at least one risk factor for disease progression to hospitalisation were included. Risk factors for disease progression were: age ≥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 and serostatus of the patients at baseline was not known. This leaves uncertainties on the efficacy and safety in individuals who are seropositive at baseline due to vaccination and/or infection. Therefore, post-hoc analysis of the primary and secondary efficacy endpoint stratified by baseline serostatus were requested as post-authorisation measure (PAM) by the EMA. This information should be submitted to Swissmedic as well (post-approval requirement).

A larger sample size was actually planned for this study, but enrolment was stopped before the predefined interim-analysis, mainly because of administrative reasons, including declining case rates, increasing availability of single-infusion monoclonal antibodies (mAbs) as an alternative to placebo, and increasing vaccination rates. Nevertheless, both the EMA and FDA considered that the study can be considered confirmatory as the blinding was not broken before data finalisation. This position is endorsed.

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Patients were randomised 1:1 to receive IV remdesivir 200 mg on Day 1 and 100 mg once daily on subsequent days for a total of 3 days (n=279) or IV placebo for 3 days (n=283), plus standard of care. Randomisation was stratified by residence in a skilled nursing facility, age (<60 vs ≥60 years), and region (US vs. ex-US).

At baseline, mean age was 50 years (with 30% of patients aged 60 or older); 52% were male and 80% were white; 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 and median viral load was 6.3 $\log_{10}$ copies/mL at baseline. Baseline characteristics were balanced between treatment groups.

Overall, the study population and the chosen primary endpoint (proportion of patients with COVID-19 related hospitalisation defined as at least 24 hours of acute care, or all-cause 28-day mortality) are largely in line with that of the pivotal studies for the recently approved mAbs.

Two patients (0.7%) in the remdesivir group and 15 (5.3%) patients in the placebo group experienced COVID-19-related hospitalisation or died, resulting in a reduction of 87% in these events for remdesivir (hazard ratio, 0.134 [95% CI, 0.031 to 0.586]; p=0.0076). No deaths were observed at Day 28. These results regarding the primary endpoint were confirmed by the results of a sensitivity analysis and a benefit of remdesivir was also observed for most secondary endpoints. There were no differences between the remdesivir group and placebo group in the development of viral load over time. The EMA expressed concerns regarding this lack of effect on viral load (proof of concept), which is shared.

4.4 Safety

The overall safety profile of remdesivir is based on data from 6958 individuals who received at least 1 dose of IV remdesivir (RDV), including 6652 with COVID-19; 175 with Ebola Virus Disease (EVD); and 131 healthy participants in the Phase 1 studies.

Safety data for the specific population with moderate COVID-19 is based on data from 962 participants who received at least 1 dose of RDV in studies GS-US-540-5774 and CO-US-540-5776 as well as from 279 participants who received at least 1 dose of remdesivir in study GS-US-540-9012.

GS-US-540-5774

Only 37.8% of the patients in the 10-day treatment group received a full 10 days of treatment. The safety findings in the 10-day treatment group are, therefore, not fully representative of 10 days treatment duration.

The most common AEs were

- remdesivir 5-day group — nausea (9.9%), diarrhoea (6.3%), and hypokalaemia and headache (each 5.2%)
- remdesivir 10-day group — nausea (9.3%), hypokalaemia (6.7%), and diarrhoea and headache (each 5.2%)

More drug-related AEs were reported in the 5-day treatment group (18.8%) as compared to the 10-day treatment group (13.0%). The most common drug related AEs were nausea (5-day 6.8%; 10-day 3.6%), ALT increased (5-day 3.7%; 10-day 2.1%), AST increased (5-day 2.6%; 10-day 2.1%), 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 (9.0%) as compared to the remdesivir groups (5-day treatment group 4.7%, 10-day treatment group 5.2%), mostly related to respiratory problems. One serious AE of heart rate decreased in the remdesivir 5-day treatment group was considered to be drug related.

Overall, 5 deaths were reported under remdesivir treatment; 2 (1.0%) in the remdesivir 5-day group, 3 (1.6%) in the remdesivir 10-day group. Based on the listing of death reports, COVID-19 and likely associated respiratory complications were the most frequent reported causes of death.

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AEs leading to study drug discontinuation were slightly more often reported in the 10-day treatment group (4.1%) compared to the 5-day treatment group (2.1%). 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%).

The frequency of Grade 3 or 4 laboratory abnormalities was reported in 12.8% and 16.2% of patients in the remdesivir 5-day and 10-day group, respectively. Platelets decreased and hyperglycaemia occurred somewhat more often in the remdesivir groups.

CO-US-540-5776

The most common adverse events in the remdesivir group were haemoglobin decreased (6.7%, placebo 4.8%), prothrombin time prolonged (5.3%, placebo 1.6%), dyspnoea (4.0%, placebo 3.2%), glomerular filtration rate decreased (4.0%, placebo 3.2%).

By Day 29, deaths were reported in similar percentages of participants in the remdesivir group and the placebo group (remdesivir 4.2%; placebo 5.1%).

GS-US-540-9012

AEs most frequently observed in this study were nausea (10.8%), headache (5.9%), diarrhoea (3.9%), cough, fatigue (each 3.6%), and anosmia (3.2%).

Study drug-related AEs were reported in more participants in the remdesivir group (12.2%) than the placebo group (8.8%), but no clear trend or pattern was observed for study drug-related AEs. Drug-related AEs reported in ≥ 2% of participants were nausea (remdesivir 6.5%; placebo group 3.5%) and chills (remdesivir 2.2%; placebo group 2.1%).

The most commonly reported SAEs under remdesivir treatment were pneumonia (0.7%) and atrial fibrillation (0.7%). Other SAEs were each reported in only 1 participant. None of the SAEs was considered by the investigator to be related to study drug.

One participant in the placebo group died due to COVID-19 disease.

Overall, data from CO-US-540-5776 (placebo-controlled), GS-US-540-5774 (SOC-controlled), and GS-US-540-9012 (outpatient placebo controlled) indicate no additional safety issues.

4.5 Final clinical 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 benign to severe disease, with the majority of patients having mild to moderate disease, including flu-like symptoms up to mild pneumonia. Some of the 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).

Since it first emerged in December 2019, the disease has spread globally. It was declared a pandemic by WHO in March 2020. In Switzerland, there are currently several monoclonal antibodies approved to treat COVID-19 in the specific group of patients with mild to moderate disease not requiring supplemental oxygen. However, not all of those are active against the various viral variants. Therefore, there remains a need for alternative treatment options for this population.

BENEFICIAL EFFECTS

Five days of remdesivir treatment resulted in an improved clinical status 11 days after treatment onset as compared to standard of care in hospitalised patients with mild to moderate COVID-19 who do not require supplemental oxygen (GS-US-540-5774). In addition, in study CO-US-540-5776, a numerical benefit on time to recovery as compared to placebo was observed in a subgroup of patients with mild to moderate disease.

In response to the preliminary decision, additional data were submitted from a phase 3 randomised, double-blind, placebo-controlled study in non-hospitalised patients (GS-US-540-9012). In this study,

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remdesivir treatment for 3 days resulted in a relevant reduction in COVID-19-related hospitalisation or all-cause mortality compared to placebo.

Remdesivir treatment was relatively well tolerated. The more extensive safety information included in the present submission did not indicate any new safety issues.

UNCERTAINTIES ON THE BENEFICIAL EFFECTS

Study GS-US-540-5774 cannot be considered a confirmatory study, due to its open-label design and the relatively subjective primary endpoint used.

Data from a relatively small subgroup of patients with mild to moderate COVID-19 not requiring supplemental oxygen from study CO-US-540-5776 indicate a numerical benefit of 10 days remdesivir treatment in time to recovery. However, statistical significance could not be demonstrated, and as the study was not powered for extensive analyses in this subgroup, these results can only be considered supportive.

The effectiveness data submitted suggest a benefit of remdesivir treatment. However, due to limited information, some methodological aspects of the analysis of the HealthVerity data are unclear, which complicates the interpretation of the outcomes. Also, a different endpoint in comparison to studies GS-US-540-5774 and CO-US-540-5776, and different treatment duration in comparison to study CO-US-540-5776 were evaluated, limiting comparability to these studies. The outcomes regarding hospital discharge were inconclusive, as the sensitivity analysis showed results that were contradictory to the results of the primary analysis of this endpoint.

UNFAVOURABLE EFFECTS

The most frequently reported AEs in the remdesivir group in the subgroup of patients with mild to moderate COVID-19 not requiring supplemental oxygen in study CO-US-540-5776 were haemoglobin decreased (6.7%, placebo 4.8%), prothrombin time prolonged (5.3%, placebo 1.6%), dyspnoea (4.0%, placebo 3.2%), and glomerular filtration rate decreased (4.0%, placebo 3.2%).

The most frequently reported AEs in the remdesivir group in study CO-US-540-5774 were nausea, diarrhoea, headache, and hypokalaemia.

Available preclinical data indicate a potential risk for renal toxicity, but this is so far not confirmed in the available safety data in humans.

BENEFIT-RISK ASSESSMENT

No reliable conclusions on the efficacy of remdesivir in the treatment of patients hospitalised with COVID-19 of moderate severity can be concluded based on study GS-US-540-5774 due to its open-label design and as bias in the assessment of the primary endpoint cannot be ruled out. This cannot be offset by the additionally provided data from real world effectiveness studies or secondary analysis of data from the CO-US-540-5776, as these do not provide the same level of evidence as results from a randomised controlled trial. These uncertainties were resolved by the additional data submitted with the response to the preliminary decision that provided robust evidence of a benefit of remdesivir in the treatment of COVID-19 in an outpatient setting. Based on these findings, the extension of the indication applied for 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 is temporarily authorised – see "Properties/Effects" section.

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 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

- with pneumonia requiring supplemental oxygen,
- 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”).

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”).

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

For patients with pneumonia requiring supplemental oxygen, the total duration of treatment should be at least 5 days and not more than 10 days.

For patients who do not require supplemental oxygen or hospitalization for COVID-19 and who are at risk of developing a severe COVID-19 course, the total duration of treatment should be 3 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

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

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, 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 Veklury as clinically appropriate. 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 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 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, 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 2 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 2: 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 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), 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 Veklury 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 Veklury 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 Veklury 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 Veklury. Grade ≥ 3 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 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 Veklury compared to placebo, with no difference observed in the incidence of bleeding events between the two groups. Prothrombin time should be monitored while receiving Veklury as clinically appropriate. In Study GS-US-540-9012, the incidence of increased prothrombin time or INR was similar in patients treated with Veklury compared to placebo.

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. 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 line Calu-3 with an EC_{50} value of 280 nM after 72 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/Extracorporeal Membrane Oxygenation (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 38.4% (208/541) 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 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 Veklury 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 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 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 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]). 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 Veklury 200 mg once daily for 1 day followed by Veklury 100 mg once daily for 2 days (for a total of 3 days of intravenously administered therapy) in 562 adult and paediatric patients (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. The baseline serostatus of the patients was unknown.

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 Veklury (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 Veklury and placebo treatment groups.

The primary endpoint was the proportion of patients with COVID-19 related hospitalisation (defined as at least 24 hours of acute care) or all-cause 28-day mortality. Events (COVID-19-related hospitalisation or all-cause 28-day mortality) occurred in 2 (0.7%) patients treated with Veklury 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.

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 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. 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 following intravenous administration 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

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).

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”.

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.

- 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.

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

Date of revision of the text

May 2022