Taiwan Food and Drug Administration

Assessment Report

Trade Name：韋如意凍晶乾燥注射劑 100 毫克/瓶 / Veklury Lyophilized Powder for Injection 100 mg/Vial

Active Ingredient：Remdesivir

License Number：MOHW-PI 027899

Applicant：香港商吉立亞醫藥有限公司台灣分公司

Approval Date：2023/06/07

Indication：
適用於治療下列病人的新型冠狀病毒疾病(COVID-19，嚴重特殊傳染性肺炎)：發生肺炎並須給予氧氣治療(開始本品治療時須使用低或高流量氧氣或其他非侵入性呼吸器)的成人與 28 天大以上且體重至少 3 公斤之兒童；不須氧氣治療但惡化成重度 COVID-19 風險較高的成人與 12 歲以上且體重至少 40 公斤之兒童。

Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in：Adults and pediatric patients (at least 28 days of age and weighting 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 pediatric patients (at least 12 years of age and weighting at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progression to severe COVID-19.

1. Background Information

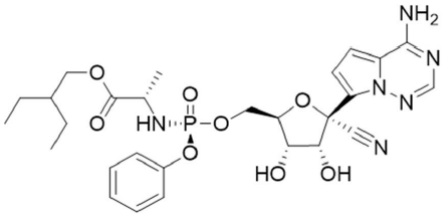
Trade Name	韋如意凍晶乾燥注射劑 100 毫克/瓶 Veklury Lyophilized Powder for Injection 100 mg/ Vial
Active Ingredient(s)	Remdesivir
Applicant	香港商吉立亞醫藥有限公司台灣分公司
Dosage Form & Strengths	凍晶乾燥注射劑 100 毫克/瓶
Indication	適用於治療下列病人的新型冠狀病毒疾病(COVID-19，嚴重特殊傳染性肺炎)：發生肺炎並須給予氧氣治療(開始本品治療時須使用低或高流量氧氣或其他非侵入性呼吸器)的成人與 28 天大以上且體重至少 3 公斤之兒童；不須氧氣治療但惡化成重度 COVID-19 風險較高的成人與 12 歲以上且體重至少 40 公斤之兒童。
Posology	**劑量** ● 對成人及體重至少 40 公斤的兒童病人，建議劑量為第 1 天靜脈輸注單劑 VEKLURY 200 毫克(起始劑量)，然後從第 2 天起每天一次靜脈輸注 VEKLURY 100 毫克(維持劑量)。 ● 對 28 天大以上，體重至少 3 公斤但未滿 40 公斤的兒童病人，建議劑量為第 1 天靜脈輸注單劑 VEKLURY 5 毫克/公斤(起始劑量)，然後從第 2 天起每天一次靜脈輸注 VEKLURY 2.5 毫克/公斤(維持劑量)。 **治療時間** ● 針對發生肺炎並須給予氧氣治療的病人，建議的治療時間為 5 天，如果病人未呈現臨床改善的效果，治療可額外延長最多 5 天，總治療時間不超過 10 天。 ● 針對不須氧氣治療但惡化成重度 COVID-19 風險較高的病人，在確診罹患 COVID-19 之後，須儘快並於出現症狀後 7 天內開始治療，總治療時間為 3 天。
Pharmacological Category **ATC Code**	J05AB16

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug Substance

The drug substance, remdesivir, is chemically designated as 2-ethylbutyl (2*S*)-2-{[(*S*)-{[(2*R*,3*S*,4*R*,5*R*)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl]methoxy}(phenoxy)phosphoryl]amino}propanoate and has the following structure:



It is a white to off-white or yellow solid. The molecular formula and the molecular weight are $C_{27}H_{35}N_6O_8P$ and 602.6 g/mol, respectively.

Adequate information of characterization of the drug substance has been provided. The molecular structure of remdesivir has been confirmed by NMR spectroscopy, mass spectrometry, elemental analysis, infrared spectroscopy, ultraviolet spectroscopy and single crystal X-Ray crystallography.

The drug substance specification includes tests for appearance, identification, clarity of solution, water content, assay, impurity content, residual solvents, organic volatile impurities and bacterial endotoxins.

2.1.2 Drug Product

The drug product contains 100 mg of remdesivir as a sterile, preservative-free lyophilized white to off-white to yellow powder in a single-dose clear glass vial. It requires reconstitution and then further dilution prior to administration by intravenous infusion. The excipients used in the drug product formulation comply with the compendial monographs.

The drug product specification includes appearance, identification, reconstitution, water content, assay, degradation product content, pH of solution, uniformity of dosage units, sterility, bacterial endotoxins and particulate matter. Analytical methods are described well and validated.

Stability studies of the drug product under long term condition (30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

In vitro antiviral assays showed that remdesivir potently inhibits SARS-CoV-2 replication in human lung cells and primary human airway epithelial cultures, with an EC_{50} of 0.01 μM; a weaker activity was observed in Vero cells (EC_{50} = 0.137-0.77 μM) and Vero E6 cells (EC_{50} = 1.65 μM). In vivo therapeutic efficacy of remdesivir against SARS-CoV-2 was demonstrated by a rhesus macaques study published by the NIH. The authors claimed that the dosing regimen (a loading dose of 10 mg/kg remdesivir, followed by a daily maintenance dose of 5 mg/kg) in monkeys mimics the daily dosing tested in clinical studies with COVID-19 patients and results in similar systemic drug exposure. Remdesivir-treated animals did not show signs of respiratory disease and had reduced pulmonary infiltrates on radiographs. Virus titers in bronchoalveolar lavages were significantly reduced as early as 12hrs after the first treatment was administered. At necropsy on day 7 after inoculation, lung viral loads of remdesivir-treated animals were significantly lower, and there was a clear reduction in damage to the lung tissue. In $Ces1c^{-/-}$ mice infected with chimeric SARS-CoV expressing the SARS-CoV-2 RNA polymerase, remdesivir treatment resulted in decreased viral loads in the lungs, decreased lung hemorrhage, and increased pulmonary function.

Remdesivir and the nucleoside analog GS-441524 were profiled for in vitro cytotoxicity and mitochondrial toxicity in multiple relevant cell types. Both remdesivir and GS-441524 exhibited > 3.5-fold margins in most in vitro toxicity assays. Data from in vitro studies with liver cell culture systems demonstrated that human hepatocytes are susceptible to remdesivir-mediated toxicity, likely due to high cellular permeability and effective intracellular metabolism of the drug. While GS-704277 and GS-441524 are in vivo metabolites and can be readily detected in plasma, these metabolites are unlikely to contribute significantly to changes in liver enzymes observed in humans treated with repeated doses of remdesivir, due to their low systemic exposure and minimal in vitro effects on hepatocytes. The enzymatic activities of human DNA polymerases α and β, as well as that of RNA polymerase II, were unaffected by GS-443902 up to 200 μM, the highest concentration tested. Molecular target screening studies with GS-441524 and GS-466547 showed no significant binding (> 50%) at 10 μM.

There were no remdesivir-related adverse findings in safety pharmacologic parameters regarding the central nervous system in rats or the cardiovascular system in monkeys up to the highest examined dose (50 and 10 mg/kg, respectively). In the in vitro hERG assay, the concentration that resulted in 20% inhibition (IC_{20}) and IC_{50} values for the inhibitory effect of remdesivir were 7.5 μM and 28.9 μM, respectively. On the other hand, increased respiration rates in rats administered with 20 and 50 mg/kg of remdesivir were noted. The NOEL was determined as 5 mg/kg.

2.2.2 Toxicological Studies

The general toxicity profile of remdesivir was evaluated in rats and monkeys. The primary effects of remdesivir were on the kidney in rats. The sensitivity of rats to renal effects of remdesivir appears to be related to the active tubular transport of remdesivir metabolites by rat renal OAT3; this interaction has not been identified with human renal OAT3. It is worthy to note that there was one remdesivir-treated (20 mg/kg/day) rhesus monkey euthanized due to remdesivir-related kidney findings in a non-GLP repeated-dose study. On the other hand, no remdesivir-related effects were noted in monkeys up to the highest dose examined (10 mg/kg/day).

Remdesivir is not considered genotoxic by a standard battery of in vitro and in vivo studies. It is acceptable that no carcinogenicity studies were conducted with remdesivir because of its short-term use. There were no effects on male reproductive performance and spermatogenesis, and the NOAEL for male reproductive toxicity was 10 mg/kg/day. For females at 10 mg/kg/day, a statistically significantly lower mean number of corpora lutea, and consequently lower mean numbers of implantation sites and viable embryos, and lower mean ovary and uterus/cervix/oviduct weights were noted, and the NOAEL for female reproductive toxicity and embryonic toxicity was 3 mg/kg/day. There were no effects on embryofetal development in rats and rabbits, and the NOAELs were 20 mg/kg/day in both species. There were no adverse effects in the pre- and postnatal toxicity study in rats, and the NOAEL was 10 mg/kg/day. An in vitro hemolytic potential and plasma compatibility study showed that remdesivir formulations were compatible with the monkey, rat, and human whole blood and plasma.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

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 minutes infusion.

Remdesivir is approximately 93% bound to human plasma proteins (ex-vivo data) with free fraction ranging from 6.4% to 7.4%. The binding is independent of drug concentration over the range of 1 to 10 μM, with no evidence for saturation of remdesivir binding. 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.

Remdesivir is extensively metabolized 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.

Following a single 150 mg IV 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.

2.3.2 Interaction Studies

Clinical drug-drug interaction studies have not been performed with remdesivir.

In vitro, remdesivir is a substrate for drug metabolizing enzyme CYP3A4, and is a substrate for Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and P-glycoprotein (P-gp) transporters. *In vitro*, remdesivir is an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1. GS-704277 is a substrate for OATP1B1 and OATP1B3. The clinical relevance of these *in vitro* assessments has not been established.

Remdesivir is not a substrate for CYP1A1, 1A2, 2B6, 2C9, 2C19, or OATP1B3. GS-704277 and GS-441524 are not substrates for CYP1A1, 1A2, 2B6, 2C8, 2C9, 2D6, or 3A5. GS-441524 is also not a substrate for CYP2C19 or 3A4. GS-704277 and GS-441524 are not substrates for OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2k. GS-441524 is also not a substrate for OATP1B1 or OATP1B3.

2.3.3 Special Populations

Pharmacokinetic differences for gender, race, and age have not been evaluated. The pharmacokinetics in paediatric patients also have not been evaluated. Using modeling and simulation, the recommended dosing regimen is expected to result in comparable steady-state plasma exposures of remdesivir and metabolites in patients 12 years of age and older and weighing at least 40 kg as observed in healthy adults.

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.

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.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

In the submission, the efficacy of Veklury was mainly supported by two pivotal studies (Study 5776 [ACTT-1] and Study 9012). Study 5776 [ACTT-1] was a Phase III, randomized, double-blind, placebo-controlled, multi-national, multi-center study in hospitalized adults diagnosed with mild/moderate to severe COVID-19. The primary efficacy endpoint was time to recovery by Day 29 ITT. The primary analysis demonstrated that patients in the Veklury group had a statistically significant shorter time to recovery than those in the placebo group, with a median of 10 days to recovery in the Veklury group versus 15 days in the placebo (HR = 1.29; 95% CI: 1.12 to 1.49; p-value < 0.001).

Study 9012 was a Phase III, randomized, double-blind, multi-national, multi-center, placebo-controlled study in high-risk non-hospitalized COVID-19 adults and pediatric patients. The primary efficacy endpoint was a composite endpoint of COVID-19-related hospitalization or all-cause death by Day 28 on FAS. The primary Cox model demonstrates an 87% risk reduction in COVID-19-related hospitalization or all-cause death with Veklury compared with placebo (HR = 0.134; 95% CI: 0.031 to 0.586; p = 0.0076).

As a result, Study 5776 [ACTT-1] have provided sufficient evidence to support the use of Veklury for the treatment of hospitalized adult patients diagnosed with COVID-19. Moreover, Study 9012 demonstrated that Veklury was effective at preventing disease progression in high-risk non-hospitalized COVID-19 adults and pediatric patients.

There were two other studies to support the efficacy in adults:
Study 5774 was open-label randomized trial to compare Veklury 5-days, Veklury 10-days to SOC in 596 patients with moderate COVID-19. The primary endpoint was clinical status assessed by 7-point ordinal scale on Day 11. Primary analysis demonstrated that treatment with Veklury for 5 days resulted in greater odds of improved clinical status at Day 11 compared with treatment with only SOC (p = 0.0174).

Study 5773 was open-label randomized trial to compare Veklury 5-days to Veklury 10-days

in 397 severe COVID-19 patients who were not mechanically ventilated. The primary endpoint was clinical status assessed by 7-point ordinal scale on Day 14. Primary analysis demonstrated that treatment with Veklury for 5 days and treatment with Veklury for 10 days resulted in similar odds of improved clinical status at Day 14 ($p = 0.1563$).

Study 5823 was a single-arm, open-label, multi-national, multi-center study in COVID-19 hospitalized pediatric patients from birth to less than 18 years of age. Interim results of 53 subjects who were at least 28 days of age and weighting at least 3 kg were provided. The clinical outcomes were secondary endpoints and descriptively analyzed. Overall, the median (Q1, Q3) change from baseline in clinical status as assessed by 7-point ordinal scale was 2.0 (1.0, 4.0) on Day 10. The median (Q1, Q3) time to recovery was 7 (5, 16) days and 60.4% of subjects were discharged by Day 10.

2.4.2 Safety Results

In Study 5776, the incidences between the RDV 10-day and placebo groups were similar in Grade 3 or higher AEs (51% versus 57%) and SAEs (25% versus 32%) by Day 29. Higher proportions of participants with severe disease had AEs, treatment-related AEs, treatment-related Grade 3 or higher AEs, SAEs, and AEs leading to premature discontinuation of study treatment compared with those with mild-to-moderate disease. The majority of AEs were generally consistent with the underlying manifestations of COVID-19.

In Part A of Study 5773 and Study 5774, the safety profiles were generally comparable between the 5-day and 10-day remdesivir treatment groups. The incidence and types of AEs were generally similar between the 2 treatment groups and were generally consistent with the manifestations of COVID-19. Serious adverse events and deaths were generally consistent with underlying manifestations of COVID-19. In Study 5774, The overall safety profile of the RDV treatment groups was similar to the SOC only group.

The incidence of all graded individual treatment-emergent laboratory abnormalities was generally similar across the RDV 10 day and placebo treatment groups, with the exception of increased prothrombin time and increased prothrombin international normalized ratio (INR), which were more common in the RDV 10-day group. The majority of abnormalities were Grade 1 or 2 (>80%). The most common Grade 3 or 4 laboratory abnormality was decreased CLcr in both groups (18% in the RDV 10-day group and 23% in the placebo group). The incidence of renal AEs increased with increasing baseline disease severity but was generally similar between the RDV and placebo groups. The same trend was observed on the incidence of hepatic AEs between the RDV and placebo groups.

The incidence of potential infusion-related reactions was 0.036% in clinical trials and

0.0057% among all sources of clinical experience.

The available data was too limited to make conclusion between exposure to RDV and adverse pregnancy or infant outcomes. The clinical experience on pediatric use was limited. A Phase 2/3 study to evaluate RDV in participants from birth to < 18 years of age with COVID-19 is ongoing.

2.5 Conclusion

This multidisciplinary review recommends approval for Veklury (Remdesivir) for the indication of treatment of COVID-19 in adults and pediatric patients (at least 28 days of age and weighting at least 3 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment), and in adults and pediatric patients (at least 12 years of age and weighting at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progression to severe COVID-19.

3. Post-Marketing Requirements

- Submit final report of Domestic Registry Study GS-TW-540-5928 after study completion**.**
-Submit the east Asian PK report. Further clarify whether the PK parameters in east Asian population is different from Western population.
- Submit final report of Study GS-US-540-5912 after study completion to support the dose adjustment in patients with renal impairment.