Summary Report of Benefit-Risk Assessment

VEKLURY LYOPHILIZED POWDER FOR IV INFUSION 100MG

VEKLURY SOLUTION FOR IV INFUSION 5MG/ML

NEW DRUG APPLICATION

Active Ingredient	Remdesivir
Product Registrant	Gilead Sciences Singapore Pte Ltd
Product Registration Number	SIN15950P, SIN15951P
Application Route	Abridged evaluation
Date of Approval	10 June 2020

Table of Contents

A INTRODUCTION

Veklury is conditionally approved for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in adult patients with oxygen saturation of ≤ 94% (room air), or those requiring oxygen inhalation, under invasive mechanical ventilation (IMV) or under extracorporeal membrane oxygenation (ECMO).

Veklury treatment is administered as a 200mg intravenous (IV) infusion on Day 1, followed by 100mg IV infusion once daily from Day 2 up to Day 10. The optimal duration of treatment of remdesivir has not been established. As a guide, the total duration of treatment is up to 10 days in patients under IMV or ECMO, up to 5 days in patients who are not under IMV or ECMO, and up to 10 days if patients do not improve.

The active substance, remdesivir, is an antiviral adenosine nucleotide prodrug that is metabolized intracellularly to active remdesivir triphosphate, which acts as an analogue of adenosine triphosphate (ATP) and competes with the natural ATP for incorporation into nascent ribonucleic acid (RNA) chains by SARS-CoV-2 RNA-dependent RNA polymerase, resulting in delayed chain termination during replication of the viral RNA.

Veklury is available as a lyophilised powder for IV infusion containing 100mg of remdesivir or a solution for IV infusion containing 5mg/mL of remdesivir. Other ingredients in the products are sulfobutylether-β-cyclodextrin sodium, water for injection, with sodium hydroxide and hydrochloric acid as pH adjusters.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, remdesivir, is manufactured at the following sites:

- Gilead Alberta ULC, Edmonton, Canada
- Cambrex Charles City Inc., Charles City, USA
- Esteve Huayi Pharmaceutical Co., Ltd., Shaoxing, China.

The drug product, Veklury Lyophilized Powder for IV Infusion 100mg, is manufactured at the following sites:

- Jubilant HollisterStier, LLC, Spokane, USA
- Patheon Manufacturing Services LLC, Greenville, USA
- Hikma Farmaceutica (Portugal) S.A., Terrugem SNT, Portugal
- Hospira, Inc., McPherson, USA.
- Patheon Italia S.p.A., Monza, Italy
- Valdepharm, Val de Reuil, France
- Xellia Pharmaceuticals USA LLC, Bedford, USA

The drug product, Veklury Solution for IV Infusion 5mg/mL, is manufactured at the following sites:

- Jubilant HollisterStier, LLC, Spokane, USA
- Patheon Manufacturing Services LLC, Greenville, USA
- Hikma Farmaceutica (Portugal) S.A., Terrugem SNT, Portugal

- Hospira, Inc., McPherson, USA
- Patheon Italia S.p.A., Monza, Italy
- Gilead Sciences, Inc., La Verne, USA

Drug substance:

The chemical synthesis was briefly described, with some information on the solvents and reagents used.

The drug substance has been appropriately characterised. The specifications are established in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q6A. Information on the qualification of impurities were not available at the point of registration. Based on published literature and reports, there was no evidence suggesting a potential risk of acute toxicity caused by the impurities. Considering the short patient exposure of 5 to 10 days and the urgent medical need, the proposed impurities limits were considered acceptable for conditional approval. The analytical methods used have been adequately described. Information on the reference standards used for identity, assay and impurities testing was presented. Additional data on the synthetic process and impurities would be required for post-registration review.

The drug substance is approved for storage at room temperature with a re-test period of 48 months.

Drug product:

Both products are manufactured using aseptic processing. The processes are considered to be standard.

Evidence of compliance with GMP (Good Manufacturing Practice) have been provided for all manufacturing sites involved. The manufacturing processes have been described in detail and adequate in-process controls are in place to ensure product quality.

The specifications are established in accordance with ICH Q6A. The impurity profiles of the products are similar to that observed in the drug substance. The analytical methods used have been adequately described. Information on the reference standards used for identity, assay and impurities testing was presented. Additional data on process validation would be required for post-registration review.

For the lyophilised powder, the approved shelf-life is 36 months when stored below 30ºC. For the concentrate solution, the approved shelf-life is 24 months when stored at 2-8ºC. The container closure system for both products are Type 1 clear glass vials with elastomeric closures, and aluminium overseal with flip-off caps.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of remdesivir in the treatment of SARS-CoV-2 infection was based primarily on the preliminary top-line data from an ongoing pivotal Phase III Adaptive coronavirus disease 2019 (COVID-19) Treatment Trial Stage 1 study, referred to as the ACTT1 study, and supported by the interim top-line data from an ongoing Phase III SIMPLE-severe study.

ACTT1 study
This was a phase III, adaptive, multicentre, randomised, placebo-controlled study comparing remdesivir with placebo in hospitalised adult patients (≥18 years of age) with confirmed SARS-CoV-2 infection (RT-PCR within the last 72 hours) who had at least one of the following: radiographic infiltrates by imaging, or oxygen saturation (SpO_2) ≤ 94% or requiring supplemental oxygen or requiring mechanical ventilation. Patients in the study were randomised in a 1:1 ratio to receive IV infusion of remdesivir 200mg on Day 1 and IV 100mg on Day 2 to 10, or matching placebo once daily for 10 days.

The primary efficacy endpoint was to demonstrate superiority of remdesivir over placebo in the time to recovery up to Day 29 and was stratified based on baseline disease severity (i.e. severe disease versus mild-moderate disease). The day of recovery was defined as the first day on which the subject satisfies one of the following categories from the ordinal scale:

- Hospitalised, not requiring supplemental oxygen, no longer requires ongoing medical care
- Not hospitalised, limitation on activities and/or requiring home oxygen
- Not hospitalised, no limitations on activities

The key secondary efficacy endpoints evaluated the odds of improvement in clinical outcome of patient at Day 15 based on an 8-point ordinal scale. The 8-point ordinal scale categories are as follow:

1. Not hospitalised, no limitations on activities
2. Not hospitalised, limitation on activities and/or requiring home oxygen
3. Hospitalised, not requiring supplemental oxygen, no longer requires ongoing medical care (this would include those kept in hospital for quarantine/infection control, awaiting bed in rehabilitation facility or homecare, etc.)
4. Hospitalised, not requiring supplemental oxygen, requiring medical care (COVID-19 related or otherwise)
5. Hospitalised, requiring supplemental oxygen
6. Hospitalised, on non-invasive ventilation or high flow oxygen devices
7. Hospitalised, on IMV or ECMO
8. Death

A total of 1,063 patients were randomised in the study: 541 patients in the remdesivir group and 522 patients in the placebo group. At the time of database cut-off April 28, 2020, the study was still ongoing, there were 132 (24.4%) of patients in the remdesivir group and 169 (32.4%) of patients in the placebo group who had not recovered and had not completed the Day 29 follow-up visit.

The mean age of patients was 58.9 years, 64.3% were male, 79.8% of patients were enrolled at sites in North America, 15.3% in Europe and 4.9% in Asia. Overall, 53.2% of the patients were White, 20.6% were Black, 12.6% were Asian and 13.6% were designated as Others or not reported, and 23.4% were Hispanic or Latino. Most patients had either one (27%) or two or more (52.1%) of the prespecified coexisting conditions at enrolment, most commonly hypertension (49.6%), obesity (37.0%) and type 2 diabetes mellitus (29.7%). The median number of days between symptom onset and randomisation was 9 (interquartile range, 6 to 12), A total of 943 (88.7%) patients had severe disease at enrolment, 272 (25.6%) patients were of ordinal scale score category 7, 197 (18.5%) category 6, 421 (39.6%) category 5, and 127 (11.9%) category 4.

The primary efficacy results showed that patients in the remdesivir group had a shorter time to recovery than patients in the placebo group (median 11 days, as compared with 15 days, rate ratio for recovery, 1.32; 95% confidence interval [CI], 1.12 to 1.55; p<0.0001). The results did not show a statistically significant survival benefit with remdesivir, although death rate was numerically lower with remdesivir compared to placebo group (5.9% vs 10.4%, HR: 0.70, 95%CI: 0.47–1.04, p=0.059).

The observed favourable results of remdesivir were driven primarily by the higher recovery rate in patients who had $SpO_2 \leq 94\%$ (room air) and requiring oxygen supplementation (baseline ordinal scale score category 5). This subgroup of patient population also had the largest sample size compared to other patient subgroups stratified by disease severity (222 patients in remdesivir group and 199 patients in placebo group). There was statistically significantly higher recovery rate ratio (rate ratio 1.47; 95%CI: 1.17-1.84) and reduction in mortality rate (hazard ratio 0.22; 95% CI: 0.08-0.58) in remdesivir group compared to placebo group.

In other patient subgroups, the clinical outcomes varied according to the disease severity, as below:

- In patients requiring non-invasive ventilation or high-flow oxygen therapy (baseline ordinal scale score category 6) (98 patients in remdesivir group and 99 patients in placebo group), there was shorter median time to recovery (16 days versus 22 days) and higher recovery rate (rate ratio 1.20; 95% CI:0.79-1.81) in remdesivir group compared to placebo. The mortality rate was similar in both treatment groups (13.2% versus 13.1%).

- In patients not requiring oxygen therapy (baseline ordinal scale score category 4) (67 patients in remdesivir group and 60 patients in placebo group), there were higher recovery rates (rate ratio 1.38; 95%CI: 0.94-2.03) and higher odds for improvement in ordinal scale score (odds ratio 1.51; 95%CI: 0.76-3.00) in remdesivir group than placebo. The mortality rate was similarly low in both treatment groups (1.5% vs 1.5%). In patients with $SpO_2 > 94\%$ and not requiring oxygen therapy (mild-moderate subgroup), there was no difference between remdesivir and placebo group in terms of recovery rate (rate ratio 1.08; 95%CI: 0.72-1.61) and odds of improvement in ordinal scale score (odds ratio 1.13; 95%CI: 0.53-2.41). As no recovery benefit with remdesivir was seen in mild-moderate subgroup (SpO_2 >94%), the 13% higher recovery observed in patients with baseline score 4 (hospitalised patients not requiring oxygen irrespective

of SpO_2) was probably contributed by those patients with $SpO_2 \leq 94\%$ without oxygen supplementation requirement. This suggests that this subgroup of patients with $SpO_2 \leq 94\%$ may potentially achieve favourable response from remdesivir treatment.

- In patients with very severe disease who required IMV or ECMO (125 patients in remdesivir group and 147 patients in placebo group), there was no significant difference between remdesivir and placebo group in terms of recovery rate (rate ratio 0.95; 95%CI: 0.64-1.42) and mortality rate (10.4% in remdesivir group versus 12.9% in placebo group). The median time to recovery was not estimable based on Day 15 results. Patients in this severely ill subgroup tend to have clinical features of hyperinflammatory milieu, high mortality rate and prolonged disease course. Based on these factors coupled with a smaller sample size of this subgroup and the immature data, the benefit of remdesivir in patients who required IMV or ECMO is inconclusive.

The subgroup analysis did not show the same magnitude of recovery benefit in Asian population (recovery rate ratio: 1.04; 95%CI: 0.68-1.57) or Asia geographical location (recovery rate ratio: 1.20; 95%CI: 0.65-2.22) subgroup as demonstrated in the overall population (recovery rate ratio: 1.32; 95%CI: 1.12-1.55). However, the data is inconclusive as the sample size in the subgroups was small and could be confounded by varying baseline characteristics and/or different clinical practices.

SIMPLE-severe study
This was a randomised, open-label study to compare clinical outcomes between 5-Day and 10-Day course of remdesivir in hospitalised adult patients with severe COVID-19 who had $SpO_2 \leq 94\%$ or require supplemental oxygen and not requiring IMV or ECMO. Patients in the study were randomised in a 1:1 ratio to receive IV infusion of remdesivir 200mg on Day 1 and IV 100mg on Day 2 to 10, or IV infusion of remdesivir 200mg on Day 1 and IV 100mg on Day 2 to 5. The primary efficacy endpoint evaluated patient's clinical status on Day 14 based on a 7-point ordinal scale.

A total of 397 patients were randomised in the study: 200 patients in the 5-Day group and 197 patients in the 10-Day group. A greater number of subjects in the 5-Day group completed the study (86%) compared to the 10-Day group (44%). The reasons for not completing the study in 5-Day group included hospital discharge (16 [8%] patients) and adverse events (9 [4%] patients). No patient in the 5-day group stopped treatment because of death. Of those who did not complete the 10-Day course, reasons included hospital discharge (68 [35%] patients), adverse events (22 [11%] patients), and death (12 [6%] patients).

At baseline, patients randomly assigned to the 10-Day group had significantly worse clinical status than those assigned to the 5-Day group (p=0.02). Of note, there were imbalances in the proportion of patients requiring non-invasive ventilation or high-flow oxygen support at baseline, with 30% of these patients in the 10-Day group and 24% in the 5-Day group. While the study was not planned to include patients requiring IMV, there were 9 (5%) of these patients randomised to the 10-Day group and 4 (2%) patients to the 5-Day group.

Overall, 65% of patients who received 5-Day course of remdesivir showed a clinical improvement of at least 2 points on the 7-point ordinal scale at Day 14, as compared with 54%

of patients who received 10-Day course. After adjustment for imbalances in baseline clinical status, patients receiving 10-Day course of remdesivir had a similar distribution in clinical status at Day 14 as that of patients receiving 5-Day course.

For other efficacy endpoints of interest, the two groups had similar outcomes after adjustment for baseline clinical status. The median duration of hospitalisation among patients discharged on or before Day 14 was 7 days (interquartile range, 6 to 10) for the 5-Day group and 8 days (interquartile range, 5 to 10) for the 10-Day group. Numerically more patients were discharged from the hospital in the 5-Day group than in the 10-Day group (60% versus 52%), and mortality rate was numerically lower (8% versus 11%). Discharge rates were higher in the overall population among patients who had symptoms for less than 10 days before receiving the first dose of remdesivir (62%) than among those who had symptoms for 10 or more days before receiving the first dose (49%).

In a post-hoc exploratory analysis to determine whether any subpopulation might have benefited from receiving more than 5 days of therapy with remdesivir, among patients receiving IMV at Day 5, 40% (10 of 25) patients in the 5-Day group had died by Day 14, as compared with 17% (7 of 41) patients in the 10-Day group. Treatment with remdesivir beyond 5 days among patients who were receiving noninvasive positive-pressure ventilation or high-flow oxygen, receiving low-flow oxygen, or breathing ambient air did not appear to improve outcomes.

Overall conclusion

Based on the ACTT1 study, the patients who benefited the most in terms of recovery, clinical improvement or survival were those who had $SpO_2 \leq 94\%$ and required oxygen supplementation without requiring non-invasive ventilation or IMV or ECMO. The subgroup of patients who had $SpO_2 \leq 94\%$ but did not require oxygen supplementation or required non-invasive ventilation had clinically meaningful benefit in terms of recovery and clinical improvement but no survival benefit. Subgroup analysis in ACTT1 study showed a lower magnitude of recovery benefit in Asian population but it was not conclusive due to the small sample size. The study was inconclusive in demonstrating efficacy in patients who required IMV or ECMO.

Exploratory analysis from SIMPLE-severe study suggested a survival benefit in continuing 10-Day remdesivir treatment in patients who deteriorated to require IMV by Day 5. Based on this, a potential benefit of 10-Day remdesivir treatment in severe COVID-19 patients requiring IMV could not be ruled out. In patients who do not require IMV by Day 5, there was no additional benefit with the 10-Day treatment compared to 5-Day treatment. These data provided support to the proposed dosing regimen of 5-Day remdesivir treatment in patients not requiring IMV or ECMO, and up to 10-Day remdesivir treatment for patients who require IMV or ECMO or do not show improvement.

Taken together, the two studies provided preliminary evidence of modest efficacy of remdesivir in COVID-19 patients with $SpO_2 \leq 94\%$ and requiring oxygen supplementation or requiring non-invasive mechanical ventilation or IMV or ECMO.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of remdesivir was based primarily on safety data derived from the ACTT1 study, comprising a total of 1,063 patients who received at least one dose of study treatment: 541 patients in the remdesivir group and 522 patients in the placebo group. A total of 180 (33.3%) patients in the remdesivir group and 185 (35.4%) patients in the placebo group received the full 10-Day course of treatment.

The SIMPLE-severe study provided clinical safety data comparison between 5-Day and 10-Day course of remdesivir treatment. A total of 172 (86%) and 86 (44%) patients completed treatment course for a median duration of 5 days and 10 days respectively.

Patients with elevated liver enzymes or impaired renal functions at baseline, as measured by aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels > 5 times upper limit of normal, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2, or serum creatinine clearance < 50 mL/min were excluded from the clinical studies.

ACTT1 study
Serious adverse events occurred in 114 (21.1%) patients in the remdesivir group and 141 (27.0%) patients in the placebo group; 4 events (2 in each group) were considered by site investigators to be related to remdesivir or placebo. There were 28 (5.2%) serious respiratory failure adverse events in the remdesivir group and 42 (8%) events in the placebo group. Acute respiratory failure, hypotension, viral pneumonia, and acute kidney injury were slightly more common among patients in the placebo group. No deaths were considered to be related to treatment assignment as judged by the site investigators.

Grade 3 or 4 adverse events occurred in 156 (28.8%) patients in remdesivir group and in 172 (33.0%) patients in the placebo group. The most common adverse events in the remdesivir group were anaemia or decreased haemoglobin (43 [7.9%] events in remdesivir group versus 47 [9.0%] events in the placebo group); acute kidney injury, decreased eGFR or creatinine clearance or increased blood creatinine (40 [7.4%] versus 38 [7.8%]); pyrexia (27 [5.0%] versus 17 [3.3%]); hyperglycemia or increased blood glucose level (22 [4.1%] versus 17 [3.3%]); and increased ALT or AST levels or both (22 [4.1%] versus 31 [5.9%]). The incidence of adverse events was not found to be significantly different between remdesivir group and placebo group. Because of the limited data, the causality of the observed adverse events remained inconclusive and could not be differentiated from the underlying disease symptoms.

SIMPLE-severe study
The percentages of patients experiencing adverse events were similar in the two groups, 70% in the 5-Day group and 74% in the 10-Day group. In all, 21% of patients in the 5-Day group and 35% in the 10-Day group had serious adverse events. Similar results were seen in the percentages of patients experiencing any grade 3 or higher adverse event: 30% in the 5-Day group and 43% in the 10-Day group.

The most common adverse events overall were nausea (10% in the 5-Day group versus 9% in the 10-Day group), acute respiratory failure (6% versus 11%), increased ALT (6% versus 8%), and constipation (7% in both groups). The discontinuation due to adverse events was

lower in the 5-Day group (4%) compared to the 10-Day group (10%) probably due to the shorter treatment period in the former.

Laboratory abnormalities of grade 3 or higher in severity occurred among 27% of patients in the 5-Day group and 34% of patients in the 10-Day group. Most abnormalities were transient, with no significant difference between the median changes in the two groups at Day 14. Grade 4 creatinine clearance reduction adverse events were reported in 12% of patients in the 10-Day group as compared with 3% of patients in the 5-Day group. Most of these patients (71%) had been receiving either IMV or noninvasive positive pressure ventilation or high-flow nasal cannula at baseline, consistent with the observation that disease severity at baseline was associated with safety outcomes.

E ASSESSMENT OF BENEFIT-RISK PROFILE

The coronavirus disease 2019 (COVID-19) is an ongoing, emerging, rapidly evolving pandemic caused by SARS-CoV-2 infection and it causes substantial morbidity and mortality. Currently, there is no therapeutic approved for COVID-19.

The data from ACTT1 study suggested that initiating treatment with remdesivir at different stages of COVID-19 disease severity had differential clinical outcomes. In patients with SpO_2 ≤ 94% not requiring oxygen therapy, higher recovery rates and higher odds of clinical improvement were observed with remdesivir. In patients requiring supplemental oxygen, remdesivir demonstrated faster time to recovery, higher recovery rates, higher clinical improvement rates and reduction in mortality rates. In patients requiring non-invasive ventilation or high flow oxygen therapy, remdesivir showed faster recovery rate and higher odds of clinical improvement compared to placebo.

In patients with very severe disease requiring IMV or ECMO, there was no significant difference between remdesivir and placebo. Preliminary results from the SIMPLE-severe study suggested that patients who progressed to requiring IMV or ECMO may have a lower death rate with 10-Day course of remdesivir compared to 5-Day course (17% vs 40%). This observation was inconclusive as it was based on an exploratory analysis in very small number of patients and was not statistically powered. In the absence of adequate data in this subgroup of severely ill patients who require IMV or ECMO, the appropriate use of remdesivir must be carefully assessed and considered only when the benefit clearly outweighs the risk.

It was observed that the recovery rate with remdesivir treatment in Asian patients was lower compared to non-Asian patients. However, the data is inconclusive because of the small sample size, and there might be confounding factors such as differences in baseline disease severity and/or different clinical practices across geographical regions.

The exploratory analysis data from SIMPLE-severe study suggested that remdesivir 5-Day course showed similar efficacy as 10-Day course in patients with severe COVID-19 who did not require IMV at Day 5, while patients who progress to require IMV at Day 5 may benefit from 10 days of remdesivir treatment.

The safety analysis comprised data from more than 1,000 patients who had received at least one dose of remdesivir. The ACTT1 and SIMPLE-severe studies excluded patients with elevated liver enzymes or impaired renal functions at baseline, as measured by AST or ALT levels > 5 times upper limit of normal, eGFR < 30 mL/min/1.73m^2 or serum creatinine clearance < 50mL/min. Adverse events of clinical interest reported with remdesivir included liver enzyme elevation, renal-related adverse events (acute kidney injury, increased serum creatinine, decreased glomerular filtration), infusion-related reactions (hypotension, nausea, vomiting), respiratory failure, prothrombin time prolongation, and thrombocytopenia.

Given the limited experience with remdesivir, appropriate clinical and laboratory monitoring including liver, renal and blood tests should be considered to allow early detection of any abnormalities or potential adverse events.

Based on the review of the limited quality, safety and efficacy data and given the urgent public health need during the COVID-19 pandemic, the preliminary benefit-risk balance of remdesivir was assessed to be favourable in the treatment of COVID-19 caused by SARS-CoV-2 infection in adult patients with $SpO_2 \leq 94\%$ (room air), or those requiring oxygen inhalation, under IMV or ECMO.

F CONCLUSION

The quality, efficacy and safety data of remdesivir is limited at the point of registration. Given the urgent public health need during the COVID-19 pandemic, Veklury is conditionally approved for the treatment of COVID-19 caused by SARS-CoV-2 infection in adult patients with oxygen saturation of ≤ 94% (room air), or those requiring oxygen inhalation, under invasive mechanical ventilation, or under extracorporeal membrane oxygenation.

As no studies in children and pregnant women were presented to HSA, no recommendation for use can be made in these populations.

The conditional approval of remdesivir will require ongoing manufacturing data and clinical studies to be submitted to HSA post-approval to ensure the continued safety and efficacy of the product.