Report on the Deliberation Results

May 7, 2020

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	(a) Veklury for Intravenous Injection 100 mg (Solution) (b) Veklury for Intravenous Injection 100 mg (Lyophilized powder)
Non-proprietary Name	Remdesivir (JAN*)
Applicant	Gilead Sciences K.K.
Date of Application	May 4, 2020

Results of Deliberation

Under the current pandemic of infection with a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), the applicant has submitted an application for approval of the product on the understanding that the product is qualified for approval based on Article 14-3, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Act No. 145 of 1960, hereinafter referred to as the "Pharmaceuticals and Medical Devices Act").

In its meeting held on May 7, 2020, the Second Committee on New Drugs discussed whether the product was qualified for Special Approval for Emergency under Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. As a result of the discussion, the Committee reached the following conclusion:

As the currently available information is limited, no definite conclusion can be drawn on the efficacy and safety of the product against the disease caused by SARS-CoV-2 infection. However, the product has a certain level of significance as a drug for emergency use in public health risk management, for the following reasons:

- Nonclinical studies have reported the antiviral activity of the product against SARS-CoV-2.
- A treatment effect of the product against the disease caused by SARS-CoV-2 infection has been suggested by the preliminary results of a multiregional phase III placebo-controlled study in patients with the disease caused by SARS-CoV-2 infection.
- The safety profile of the product shown by clinical studies, etc., is considered acceptable.

Based on the above, the Committee concluded that the product may be approved with the conditions listed below.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. The drug substance is classified as a powerful drug.

Approval Conditions

(1) The applicant is required to develop and appropriately implement a risk management plan.

(2) The product is granted Special Approval for Emergency, in accordance with the provisions in Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. There is extremely limited clinical experience with the product. Therefore, after the market launch, the applicant is required to promptly collect the efficacy and safety data of the product (e.g., adverse drug reaction information) from all patients treated with the product, wherever possible, until data are gathered from a certain number of patients, and to take necessary actions to ensure the proper use of the product. The applicant is also required to periodically report the information obtained.

(3) The applicant is required to take actions necessary for the proper use of the product, based on the results of an additional safety assessment of the product.

(4) The applicant is required to take actions so that the updated efficacy and safety information on the product is easily accessible to healthcare professionals.

(5) The applicant is required to request that physicians administer the product only to patients considered eligible for treatment with the product who, or whose legally acceptable representatives, have been provided with the efficacy and safety information of the product in written form, and who have provided written informed consent before the treatment.

(6) Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act (Ministry of Health and Welfare [MHW] Ordinance No.1 of 1961), the grace period for data submission is 9 months after the approval. The applicant is required to submit results of the currently ongoing clinical studies at the earliest convenience when they become available. The applicant is also required to submit other data to Pharmaceuticals and Medical Devices Agency (PMDA) at the latest within 9 months after the approval. If newly submitted data, etc., necessitate any change in the approved product information, a change in the approved product information may be ordered in accordance with the provision in Article 74-2, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

**Japanese Accepted Name (modified INN)*

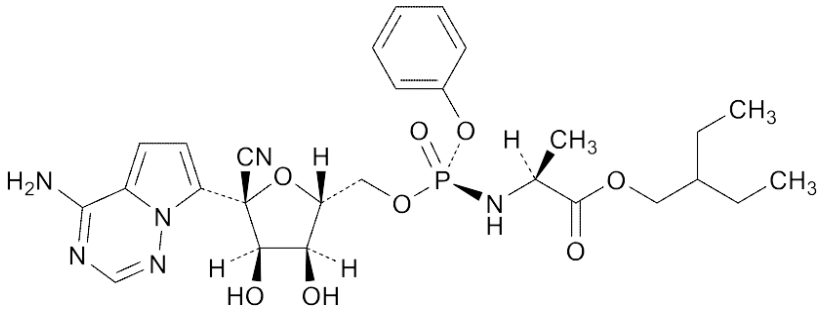
Report on Special Approval for Emergency

May 5, 2020
Pharmaceuticals and Medical Devices Agency

The following is an outline of the document prepared by Pharmaceuticals and Medical Devices Agency (PMDA) on the following pharmaceutical product submitted for marketing approval.

Brand Name	(a) Veklury for Intravenous Injection 100 mg (Solution) (b) Veklury for Intravenous Injection 100 mg (Lyophilized powder)
Non-proprietary Name	Remdesivir
Applicant	Gilead Sciences K.K.
Date of Application	May 4, 2020
Dosage Form/Strength	(a) Injectable solution: Each 20 mL vial contains 100 mg of remdesivir (b) Lyophilized powder for reconstitution for injection: Each vial contains 105 mg[1)] of remdesivir
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{27}H_{35}N_6O_8P$

Molecular weight: 602.58

Chemical name: 2-Ethylbutyl *N*-{(*S*)-[2-*C*-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-2,5-anhydro-D-altrononitril-6-*O*-yl]phenoxyphosphoryl}-L-alaninate

1) Each vial contains an overfill of 5% of the labeled amount.

Items Warranting Special Mention

The product is handled as a product that requires approval from the Minister of Health, Labour and Welfare prescribed in Article 14, Paragraph 1 of the Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 1 of the Act. Accordingly, the applicant submitted only data on clinical studies for the present application in accordance with Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act. Data on quality, nonclinical studies, etc. were not submitted. This report is a summary of the submitted data, and it is different from the review report describing the results of review.

This report was prepared based on the notification issued by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare (MHLW) (PSEHB/PED Notification No. 0423-9, dated April 23, 2020).

Office in Charge Office of New Drug IV

Attachment

Report on Special Approval for Emergency

May 5, 2020

I. Product Submitted for Approval

Brand Name	(a) Veklury for Intravenous Injection 100 mg (Solution) (b) Veklury for Intravenous Injection 100 mg (Lyophilized powder)
Non-proprietary Name	Remdesivir
Applicant	Gilead Sciences K.K.
Date of Application	May 4, 2020
Dosage Form/Strength	(a) Injectable solution: Each 20 mL vial contains 100 mg of remdesivir (b) Lyophilized powder for reconstitution for injection: Each vial contains 105 mg[2)] of remdesivir
Proposed Indication	Disease caused by SARS-CoV-2 infection (COVID-19)

Proposed Dosage and Administration

The usual dosage for adults and children weighing ≥40 kg is 200 mg of remdesivir infused intravenously on Day 1, followed by once-daily intravenous infusion of 100 mg from Day 2 onward. The usual dosage for children weighing <40 kg is 5 mg/kg of remdesivir infused intravenously on Day 1, followed by once-daily intravenous infusion of 2.5 mg/kg from Day 2 onward. The total duration of remdesivir therapy is ≤10 days.

Items Warranting Special Mention

The product is handled as a product that meets the approval standards prescribed in Article 14, Paragraph 1 of the Pharmaceuticals and Medical Devices Act based on Article 14-3, Paragraph 1 of the Act. For the present application, the applicant submitted only limited data regarding clinical studies with the expectation that a certain grace period would be granted for submitting application data pursuant to Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act. Data on quality, nonclinical studies, etc. were not submitted.

2) Each vial contains an overfill of 5% of the labeled amount.

II. Outline of Submitted Data

Gilead Sciences, Inc., in the U.S. submitted the product application for Emergency Use Authorization, and was granted the authorization on May 1, 2020 in the U.S. Accordingly, the applicant submitted an application for Special Approval for Emergency prescribed in Article 14, Paragraph 1 of the Pharmaceuticals and Medical Devices Act based on Article 14-3, Paragraph 1 of the Act. The following data were submitted for the present application: Application data for Emergency Use Authorization submitted to the U.S. Food and Drug Administration (FDA), FACT SHEET FOR HEALTH CARE PROVIDERS[3)] prepared upon the issuance of Emergency Use Authorization by the U.S. FDA, an interim report on the compassionate use experience of the product, the Investigator's Brochure, and the package insert (draft).

Table of Contents

List of Abbreviations

See Appendix.

3) Document containing text corresponding to the U.S. labeling.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Coronavirus is an RNA virus that belongs to the family *Coronaviridae*. Coronaviruses known to infect humans include 4 types that commonly infect humans, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV). On December 31, 2019, pneumonia of unknown cause occurring in Wuhan City, Hubei Province, China was reported to the World Health Organization (WHO). On January 12, 2020, WHO identified the pneumonia as a disease caused by a novel coronavirus, the target pathogen of remdesivir in the present application.[4] On January 30, 2020, WHO declared[5] Public Health Emergency of International Concern[6] on the occurrence of the pneumonia associated with the novel coronavirus in Wuhan and, on February 11, 2020, named the virus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease caused by SARS-CoV-2 as coronavirus disease (COVID-19).[7]

In Japan, the first patient infected with SARS-CoV-2 was identified on January 15, 2020. On February 1, 2020, COVID-19[8] was classified as a Designated Infectious Disease[9] pursuant to the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (Infectious Diseases Control Act) and as a Quarantinable Infectious Disease[10] pursuant to the Quarantine Act. On April 7, 2020, the Japanese government declared a state of emergency based on the amended Act on Special Measures for Pandemic Influenza and New Infectious Diseases Preparedness and Response.[11]

As of May 5, 2020, 3,489,053 people are reported to have been infected with SARS-CoV-2 globally and 241,559 of them have died.[12] In Japan, as of May 4, 2020, 15,069 people have been infected (9,007 patients, 961 asymptomatic pathogen carriers, and 5,101 people with laboratory confirmed infection [the presence or absence of symptoms is to be confirmed]). In addition, 11 patients and 4 asymptomatic pathogen carriers were identified among people who returned to Japan from abroad via charter flights. At the airport quarantine, 35 patients and 112 asymptomatic pathogen carriers were identified. In total, 15,231 have been infected, 521 of whom have died.[13]

There are the following reports on COVID-19, but the actual situation of the disease largely remains unknown.

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4) WHO: https://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/ (as of May 5, 2020)

5) WHO: https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov) (as of May 5, 2020)

6) The term Public Health Emergency of International Concern is defined in the International Health Regulations of WHO as:
(a) An extraordinary event which is determined to constitute a public health risk to other States through the international spread of disease
(b) An extraordinary event which is determined to potentially require a coordinated international response

7) WHO: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and the-virus-that-causes-it (as of May 5, 2020)

8) Limited to the disease caused by the novel coronavirus of genus *Betacoronavirus* that was reported as transmissible to humans to WHO from the People's Republic of China in January 2020)

9) The term Designated Infectious Disease means already known infectious diseases (excluding Class I Infectious Diseases, Class II Infectious Diseases, Class III Infectious Diseases, and Novel Influenza Infection, etc.) specified by Cabinet Order as a disease which would be likely to seriously affect the health of the public in the event of its spread if the provisions of the Infectious Diseases Control Act, in whole or in part, did not apply mutatis mutandis (Article 6 of the Infectious Diseases Control Act).

10) The term Quarantinable Infectious Disease means diseases specified by Cabinet Order as those which require inspection in order to prevent pathogens of infectious diseases not endemic to Japan from entering the country (Article 2, Item 3 of the Quarantine Act).

11) The state of emergency was declared over the period from April 7 through May 6, 2020 covering the following prefectures: Saitama, Chiba, Tokyo, Kanagawa, Osaka, Hyogo, and Fukuoka. On April 16, 2020, the area was expanded to the entire Japan and, on May 4, 2020, the end date was extended to May 31, 2020.

12) WHO: https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (as of May 5, 2020)

13) Ministry of Health, Labour and Welfare: https://www.mhlw.go.jp/stf/newpage_11171.html (as of May 5, 2020)

In China, the age distribution of infected people was reported as follows: <10 years old, 1%; 10 to 19 years old, 1%; 20 to 29 years old, 8%; 30 to 79 years old, 87%; and ≥80 years old, 3%. In addition, 81% of the patients had mild disease (i.e., nonpneumonia or mild pneumonia), 14% had severe disease (i.e., dyspnoea, respiratory frequency ≥30/min, blood oxygen saturation ≤93%, the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen [P/F ratio] <300, and/or lung infiltrates >50% within 24-48 hours), and 5% had very severe disease (i.e., respiratory failure, septic shock, and/or multiorgan failure). The overall mortality was 2.3%, with a mortality of 14.8% in those ≥80 years old, 8.0% in those 70 to 79 years old, and 49.0% among those with very severe disease (*JAMA.* 2020;323:1239-42).

Shown below are details of 516 patients with COVID-19 confirmed by polymerase chain reaction [PCR]) in Japan reported by the National Epidemiological Surveillance of Infectious Diseases and the Active Epidemiological Investigation (As of March 23, 2020, National Institute of Infectious Diseases, https://www.niid.go.jp/niid/ja/covid-19/9533-covid19-14-200323.html [as of May 5, 2020]).

Gender:
285 men, 231 women
Age (median [range]):
60 [1, 97] years
Age distribution: 6 patients aged <10 years (1.2%), 3 patients aged 10-19 years (0.6%), 46 patients aged 20-29 years (8.9%), 52 patients aged 30-39 years (10.1%), 59 patients aged 40-49 years (11.4%), 87 patients aged 50-59 years (16.9%), 98 patients aged 60-69 years (19.0%), 124 patients aged 70-79 years (24.0%), 39 patients aged 80-89 years (7.6%), 2 patients aged ≥90 years (0.4%)
Main symptoms[a)]:
Pyrexia, 375 of 475 patients (79%); cough, 353 of 465 patients (76%); pneumonia, 245 of 387 patients (63%); general malaise, 182 of 389 patients (47%); pharyngodynia, 115 of 393 patients (29%); nasal discharge/nasal congestion, 79 of 321 patients (25%); headache, 71 of 301 patients (24%); diarrhoea, 65 of 336 patients (19%); arthralgia/myalgia, 42 of 310 patients (14%); nausea/vomiting, 20 of 318 patients (6%); acute respiratory distress syndrome (ARDS), 10 of 277 patients (4%); conjunctival hyperaemia, 6 of 283 patients (2%)
Clinical interventions[a)]:
ICU admission, 35 of 323 patients (11%); invasive ventilation (e.g., endotracheal intubation), 49 of 347 patients (14%)
Other interventions
Extracorporeal membrane oxygenation (ECMO), 18 patients (2 patients aged 40-49 years, 5 patients aged 60-69 years, 9 patients aged 70-79 years, 2 patients aged 80-89 years)

[a)] Patients whose information was unavailable or unknown were excluded from the denominator.

Remdesivir is metabolized in the body by hydrolysis and other conversions into an analog of adenosine triphosphate, which exhibits antiviral activity by inhibiting RNA polymerase, an enzyme essential for the replication of RNA viruses. In an *in vitro* study, remdesivir has demonstrated antiviral activity against SARS-CoV-2 [see Section 3.2] and, in Japan and other countries, multiple clinical studies are being conducted to evaluate remdesivir therapy against COVID-19.

As of May 5, 2020, remdesivir has not been approved either in Japan or other countries. On May 1, 2020, remdesivir obtained Emergency Use Authorization in the U.S.

In response to the Emergency Use Authorization issued by FDA, the applicant has submitted an application for Special Approval for Emergency of remdesivir with the premise that remdesivir is qualified as a drug for approval under the provision of Article 14, Paragraph 1 of the Pharmaceuticals

and Medical Devices Act based on Article 14-3, Paragraph 1 of the Act. This report is an expedited summary of the data submitted in accordance with the notification issued by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW (PSEHB/PED Notification No. 0423-9, dated April 23, 2020).

2. Results of Main Clinical Studies

The applicant submitted the following clinical data for the present application: Preliminary results[14] of 2 clinical studies in patients with COVID-19 and information obtained from an experience of compassionate use of remdesivir.

2.1 Multiregional phase III study[15] (ACTT study, NCT04280705, Preliminary results [ongoing since February 2020])

A placebo-controlled, randomized, double-blind, parallel-group study in patients aged ≥18 years with COVID-19 (target sample size, 400 patients [200 per group]) is being conducted to investigate the efficacy and safety of remdesivir at 69 study sites in 10 countries: U.S., Denmark, Germany, Greece, Japan, Korea, Mexico, Spain, U.K., and Singapore. Table 1 shows the main inclusion/exclusion criteria of the study.

Table 1. Main inclusion/exclusion criteria

Inclusion criteria	1. Currently hospitalized with symptoms suggestive of COVID-19. 2. Has SARS-CoV-2 infection confirmed by PCR or other assays, as documented by either of the following: • PCR positive in a sample collected <72 hours prior to randomization; OR • PCR positive in a sample collected ≥72 hours prior to randomization, documented inability to obtain a repeat sample, AND progression of symptoms suggestive of SARS-CoV-2 infection. 3. At least one of the following: • Pneumonia pattern by chest x-ray, CT scan, etc., OR • SpO_2 ≤94% on room air, OR • Requiring supplemental oxygen, OR • Requiring mechanical ventilation.
Exclusion criteria	1. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times the upper limit of normal 2. Estimated glomerular filtration rate (eGFR) <30 mL/min (including patients receiving hemodialysis or hemofiltration) 3. Pregnancy or breast feeding 4. To be discharged or transferred to another hospital within 72 hours

Remdesivir (200 mg) or placebo was administered intravenously on Day 1, followed by once-daily intravenous administration of remdesivir 100 mg or placebo on Days 2 through 10. Remdesivir was discontinued upon discharge.

The primary efficacy endpoint was time to recovery[16] within 28 days after randomization.

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14) Described in FACT SHEET FOR HEALTH CARE PROVIDERS (https://www.fda.gov/media/137566/download [as of May 5, 2020])

15) ClinicalTrial.gov (NCT04280705) [https://clinicaltrials.gov/ct2/show/NCT04280705 (as of May 5, 2020)], FDA FACT SHEET FOR HEALTH CARE PROVIDERS [https://www.fda.gov/media/137566/download (as of May 5, 2020)], NIH press release (https://www.nih.gov/news-events/news-releases/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19)

16) The clinical status was assessed according to the following 8-point ordinal scale: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or ECMO; 3) Hospitalized, on non-invasive ventilation or high flow oxygen; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen - requiring continuous medical care for COVID-19 or other conditions; 6) Hospitalized, not requiring supplemental oxygen - no longer requires continuous medical care; 7) Discharged, limitation on activities and/or requiring home oxygen; 8) Discharged, no limitations on activities. "Recovery" was defined as the status meeting the conditions 6) to 8).

A total of 1,063 patients were randomized to the remdesivir group or to the placebo group at a 1:1 ratio. Table 2 shows the results of preliminary analysis of the primary endpoint, etc., conducted after 606 patients had recovered.

Table 2. Results of preliminary analysis of primary endpoint, etc.

	Remdesivir	Placebo	Hazard ratio [95% CI]	*P* value
Time to recovery (median)	11 days	15 days	1.31 [1.12, 1.54]	$P < 0.001$
Mortality	8.0%	11.6%	-	$P = 0.059$

-: Not applicable

The submitted data do not contain safety information.

2.2 Multiregional phase III study[17] (Study GS-US-540-5773, NCT04292899, Preliminary results [ongoing since March 2020])

A clinical study consisting of a randomized, open-label, parallel-group part (Part A[18]) and an open-label part (Part B) is being conducted in patients with severe COVID-19 who are ≥12 and <18 years old weighing ≥40 kg or ≥18 years old (target sample size, approximately 2,400 subjects [400 in Part A (200 per group), 2,000 in Part B,]), to investigate the efficacy and safety of remdesivir at 181 study sites in 15 countries or regions: U.S., China, France, Germany, Hong Kong, Italy, Japan, Korea, Netherlands, Singapore, Spain, Sweden, Switzerland, Taiwan, and U.K. Only the preliminary results of Part A are available currently. Table 3 shows the main inclusion/exclusion criteria of Part A.[19]

Table 3. Main inclusion/exclusion criteria

Inclusion criteria	1. SARS-CoV-2 infection confirmed by PCR ≤4 days before randomization 2. Currently hospitalized 3. SpO2 ≤94% (on room air) or requiring supplemental oxygen at screening 4. Pulmonary infiltrates on radiographic imaging
Exclusion criteria	1. Evidence of multiorgan failure 2. Mechanically ventilated (including V-V ECMO) for ≥5 days, or any duration of V-A ECMO. 3. ALT or AST >5 times the upper limit of normal 4. Creatinine clearance <50 mL/min using the Cockcroft-Gault formula for patients aged ≥18 years and Schwartz Formula for patients aged <18 years 5. Pregnancy test-positive 6. Breast-feeding

Patients were randomized to receive remdesivir for up to 5 days (5-day treatment group) or up to 10 days (10-day treatment group).

In the 5-day treatment group, 200 mg of remdesivir was administered intravenously on Day 1, followed by once-daily intravenous administration of 100 mg on Days 2 through 5. In the 10-day treatment group, 200 mg of remdesivir was administered intravenously on Day 1, followed by once- daily intravenous administration of 100 mg on Days 2 through 10. Remdesivir was discontinued upon discharge.

17) ClinicalTrial.gov (NCT04292899) [https://clinicaltrials.gov/ct2/show/NCT04292899 (as of May 5, 2020)], Gilead Sciences, Inc. press release [https://www.gilead.com/news-and-press/press-room/press-releases/2020/4/gilead-announces-results-from-phase-3-trial-of-investigational-antiviral-remdesivir-in-patients-with-severe-covid-19 (as of May 5, 2020)], FDA FACT SHEET FOR HEALTH CARE PROVIDERS [https://www.fda.gov/media/137566/download (as of May 5, 2020)]

18) The applicant explained that Part A was conducted at 55 study sites in 8 countries or regions (U.S., Germany, Hong Kong, Italy, Korea, Singapore, Spain, and Taiwan) and did not include Japanese patients.

19) Part B included patients on mechanical ventilation.

A total of 397 randomized patients who received at least 1 dose (200 in the 5-day treatment group, 197 in the 10-day treatment group) were included in the efficacy analysis population and the safety analysis population.

The primary efficacy endpoint was the clinical status on Day 14 after randomization, assessed by the 7-point ordinal scale (Table 4). Results showed that the odds ratio of improvement in clinical status in the 10-day treatment group to that in the 5-day treatment group was 0.76 [95% confidence interval (CI): 0.51, 1.13].

Table 4. Seven-point ordinal scale

Score	Scale
1	Death
2	Hospitalized, on invasive mechanical ventilation or ECMO
3	Hospitalized, on non-invasive ventilation or high flow oxygen
4	Hospitalized, on low flow supplemental oxygen
5	Hospitalized, not requiring supplemental oxygen, but requiring continuous medical care for COVID-19 or other conditions
6	Hospitalized, not requiring supplemental oxygen or continuous medical care (other than per protocol treatment with remdesivir)
7	Discharged

The time to discharge for 50% of patients was 10 days in the 5-day treatment group and 11 days in the 10-day treatment group. On Day 14, the percentage of patients with clinical improvement[20)] in the 5- and 10-day treatment groups were 65% (129 of 200 patients) and 54% (107 of 197 patients), respectively, the percentage of patients with recovery[21)] was 70% (140 of 200 patients) and 59% (116 of 197 patients), respectively, and mortality was 8% (16 of 200 patients) and 11% (21 of 197 patients), respectively.

As for safety,[22)] adverse events were reported in 71% (141 of 200 patients) in the 5-day treatment group and 74% (145 of 197 patients) in the 10-day treatment group, serious adverse events considered causally related to remdesivir were reported in 2% (3 of 200 patients) and 2% (4 of 197 patients), respectively, and Grade ≥3 adverse events considered causally related to remdesivir were reported in 4% (8 of 200 patients) and 5% (10 of 197 patients), respectively. Adverse events leading to treatment discontinuation were reported in 5% (9 of 200 patients) in the 5-day treatment group and in 10% (20 of 197 patients) in the 10-day treatment group.[23)]

2.3 Compassionate use experience of remdesivir (ongoing since January 25, 2020; data cut-off, [redacted], 2020)

Data from 163 patients with COVID-19 who received at least 1 dose of remdesivir between January 25, 2020 and [redacted], 2020 were collected. The number of patients[24)] receiving remdesivir in each country was as follows: 84 patients in Italy, 46 patients in the U.S., 9 patients in Japan, 5 patients in France, 4 patients in Switzerland, 3 patients each in Austria and U.K., 2 patients each in Germany, Ireland, and Spain, and 1 patient each in Canada, Greece, and Netherlands.

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20) Defined as an improvement of ≥2 points from baseline on a predefined 7-point ordinal scale.
21) Defined as no longer requiring oxygen support or discharge from the hospital.
22) Terms of adverse events other than "hepatic enzyme increased" are not specified in the submitted data. For hepatic enzyme increased, see Section 3.3.1.
23) The applicant explained that all-cause mortality up to Day 28 was 10% (19 of 200 patients) in the 5-day treatment group and 13% (25 of 197 patients) in the 10-day treatment group.
24) Information on race was not collected.

Remdesivir 200 mg was administered intravenously on Day 1, followed by once-daily intravenous administration of 100 mg on Days 2 through 10. Patients were allowed to receive standard of care at the discretion of the physician.

Of 163 patients, 116 completed the 10-day treatment. The treatment duration in the remaining patients was 5 to 9 days in 32 patients and ≤4 days in 15 patients. The follow-up period was ≤4 days in 2 patients, 5 to 9 days in 21 patients, 10 to 15 days in 64 patients, and ≥16 days in 76 patients.

Table 5 shows the patient inclusion/exclusion criteria. As shown in the table, the criteria were changed to stricter ones with the increase in the number of patients who want to receive remdesivir treatment relative to the limited supply of the drug. The criteria for discontinuation were (1) alanine aminotransferase (ALT) ≥5 times the upper limit of normal or (2) creatinine clearance estimated by the Cockcroft-Gault equation <30 mL/min.

Table 5. Patient inclusion/exclusion criteria

Date of change	Inclusion criteria	Exclusion criteria
■■, 2020	• Currently hospitalized • PCR positive for SARS-CoV-2 • Oxygen saturation <94% or NEWS2 score >4	• Multiorgan failure
■■, 2020	• Currently hospitalized • PCR positive for SARS-CoV-2 • Oxygen saturation <94% or NEWS2 score >4	• Multiorgan failure • Invasive mechanical ventilation • Co-administration of lopinavir/ritonavir • AST or ALT >5 times the upper limit of normal • Pregnancy
■■, 2020	• Currently hospitalized • PCR positive for SARS-CoV-2 • Oxygen saturation <94% or NEWS2 score >4	• Multiorgan failure • Co-administration of lopinavir/ritonavir • AST or ALT >5 times the upper limit of normal • Creatinine clearance <30 mL/min • Pregnancy
■■, 2020	• Currently hospitalized • PCR positive for SARS-CoV-2 • Oxygen saturation <94% or NEWS2 score >4 or requiring supplemental oxygen • Invasive mechanical ventilation	• Multiorgan failure • Co-administration of lopinavir/ritonavir • ALT >5 times the upper limit of normal • Creatinine clearance <30 mL/min • Pregnancy
March 2, 2020	• Currently hospitalized • PCR positive for SARS-CoV-2 • Oxygen saturation ≤94%, requiring supplemental oxygen, or NEWS2 score ≥4	• Multiorgan failure • Co-administration of lopinavir/ritonavir • Continuously requiring a vasopressor • ALT >5 times the upper limit of normal • Creatinine clearance <30 mL/min, receiving hemodialysis or continuous veno-venous hemodiafiltration • Pregnancy

NEWS2: National Early Warning Score 2 (updated report of a working party London: RCP, 2017)

Table 6 shows the oxygen support status[25)] before and after remdesivir treatment. Oxygen support status improved by ≥1 level in 47.2% (77 of 163) of patients. Death occurred in 20.2% (33) of patients.

[25)] Classified according to the following categories: Death, Invasive (invasive mechanical ventilation or ECMO), Noninvasive (high-flow oxygen or noninvasive positive pressure ventilation), Low-flow oxygen, Room air, or Discharged.

Table 6. Oxygen support status before and after remdesivir treatment

		Oxygen support status before remdesivir treatment[c)]			
		Invasive[a)] (N = 104)	Noninvasive[b)] (N = 24)	Low-flow oxygen (N = 31)	Room air (N = 3)
Oxygen support status after remdesivir treatment	Death	27 (26)	5 (21)	1 (3)	0
	Invasive[a)]	39 (38)	5 (21)	1 (3)	0
	Noninvasive[b)]	8 (8)	4 (17)	0	0
	Low-flow oxygen	6 (6)	1 (4)	3 (10)	0
	Room air	12 (12)	0	2 (7)	0
	Discharged	12 (12)	9 (38)	24 (77)	3 (100)
	Improved	38 (37)	10 (42)	26 (84)	3 (100)

n (%)
a) ECMO or invasive mechanical ventilation
b) Noninvasive positive pressure ventilation or high-flow oxygen
c) One patient with unknown oxygen support status before and after remdesivir treatment was discharged.

Among 9 patients who received remdesivir in Japan[26)] (8 on invasive ventilation, 1 on low-flow oxygen therapy), 6 achieved ≥1 level of improvement in oxygen support status, and 1 patient died.[27)]

As for safety, adverse events were reported in 50.3% (82 of 163) of patients, and serious[28)] adverse events were reported in 23.3% (38 of 163) of patients. Tables 7 and 8 show the main observed events. Adverse events leading to treatment discontinuation were reported in 13 patients (renal failure in 3 patients, ALT increased in 2 patients, acute renal disorder in 2 patients, multiple organ dysfunction syndrome in 2 patients, hepatitis,[29)] liver function tests increased, renal tubular necrosis, systolic dysfunction, respiratory distress, rash maculo-papular, rash, aspartate aminotransferase (AST) increased, renal creatinine/clearance abnormal, and hypotension in 1 patient each [including duplicate counting]). Hepatitis,[29)] liver function tests increased, acute renal disorder, rash, and hypotension were considered to be causally related to remdesivir.

[26)] According to the applicant, [redacted].
[27)] A 7[redacted]-year-old man (race unknown). Baseline SpO_2 86%, ECMO started on the day remdesivir was initiated. Comorbidity unknown. Adverse events: Death, disseminated intravascular coagulation, atrial fibrillation, pneumothorax, hypotension, haemorrhage, haemoptysis, renal dysfunction, hepatic enzyme increased, blood bilirubin increased, and hypernatraemia.
[28)] Defined according to the criteria specified in Prescriber's Agreement.
[29)] Two episodes of the same event occurred in a single patient.

Table 7. Adverse events reported in ≥2% of patients

Event	Baseline oxygen support status		Total (N = 163)
	Invasive ventilation (N = 104)	Noninvasive oxygen therapy (N = 58)	
Total	58 (55.8)	24 (41.4)	82 (50.3)
Anaemia	1 (1.0)	2 (3.4)	3 (1.8)
Diarrhoea	1 (1.0)	6 (10.3)	7 (4.3)
Nausea	0	2 (3.4)	2 (1.2)
Multiple organ dysfunction syndrome	5 (4.8)	0	5 (3.1)
Pyrexia	2 (1.9)	2 (3.4)	4 (2.5)
Coronavirus infection	6 (5.8)	1 (1.7)	7 (4.3)
Septic shock	3 (2.9)	1 (1.7)	4 (2.5)
Pneumonia	3 (2.9)	0	3 (1.8)
Transaminases increased	5 (4.8)	3 (5.2)	8 (4.9)
ALT increased	3 (2.9)	2 (3.4)	5 (3.1)
AST increased	3 (2.9)	2 (3.4)	5 (3.1)
Hepatic enzyme increased	3 (2.9)	2 (3.4)	5 (3.1)
Hypernatraemia	3 (2.9)	0	3 (1.8)
Acute renal dysfunction	7 (6.7)	1 (1.7)	8 (4.9)
Renal failure	4 (3.8)	1 (1.7)	5 (3.1)
Renal dysfunction	5 (4.8)	0	5 (3.1)
Respiratory failure	10 (9.6)	1 (1.7)	11 (6.7)
Acute respiratory distress syndrome	4 (3.8)	1 (1.7)	5 (3.1)
Respiratory distress	0	2 (3.4)	2 (1.2)
Rash	3 (2.9)	2 (3.4)	5 (3.1)
Hypotension	7 (6.7)	1 (1.7)	8 (4.9)
Deep vein thrombosis	3 (2.9)	0	3 (1.8)

n (%)
One patient with unknown oxygen support status before and after remdesivir treatment was excluded from the subpopulation analysis classified by baseline oxygen therapy, but was included in the analysis of the entire population.

Table 8. Serious adverse events reported in ≥2 patients

Event	Baseline oxygen support status		Total (N = 163)
	Invasive ventilation (N = 104)	Noninvasive oxygen therapy (N = 58)	
Respiratory failure	9 (8.7)	1 (1.7)	10 (6.1)
Acute respiratory distress syndrome	2 (1.9)	1 (1.7)	3 (1.8)
Respiratory distress	0	2 (3.4)	2 (1.2)
Coronavirus infection	5 (4.8)	0	5 (3.1)
Septic shock	2 (1.9)	1 (1.7)	3 (1.8)
Pneumonia	2 (1.9)	0	2 (1.2)
Sepsis	1 (1.0)	1 (1.7)	2 (1.2)
Acute renal dysfunction	6 (5.8)	0	6 (3.7)
Renal failure	3 (2.9)	1 (1.7)	4 (2.5)
Hypotension	6 (5.8)	0	6 (3.7)
Multiple organ dysfunction syndrome	3 (2.9)	0	3 (1.8)

n (%)
One patient with unknown oxygen support status before and after remdesivir treatment was excluded from the subpopulation analysis classified by baseline oxygen therapy, but was included in the analysis of the entire population.

Among 9 patients[26] receiving remdesivir in Japan, 5 experienced adverse events (renal dysfunction, hypotension[29]/atrial fibrillation[30]/renal dysfunction[29]/hypernatraemia/hepatic enzyme increased/disseminated intravascular coagulation/haemorrhage/blood bilirubin increased/haemoptysis/pneumothorax, ALT increased/AST increased/amylase increased, hypernatraemia/hepatic enzyme increased/renal dysfunction/myoclonus/diarrhoea/deep vein thrombosis/cardiac arrest, pruritus). Serious adverse events were reported in 2 patients[31]

[30] Five episodes of atrial fibrillation occurred in single patient.
[31] Baseline oxygen therapy was ECMO or invasive mechanical ventilation.

(hypotension[29])/disseminated intravascular coagulation/haemorrhage/pneumothorax, cardiac arrest), but all of them were unrelated to remdesivir.

Data from 53 patients who received remdesivir on a compassionate basis on or before March 7, 2020, are summarized in the literature (*N Engl J Med*. 2020 Apr 10, doi:10.1056/NEJMoa2007016).

3. Current Summary of the Submitted Data

The submitted data show that there is limited information available currently, precluding a definite conclusion regarding the quality, efficacy, or safety of remdesivir. Clinical studies of remdesivir are currently ongoing. The applicant was given a grace period to submit some data for the present application. When such data, including results of the ongoing clinical studies, are submitted, the quality, efficacy, and safety of remdesivir should be further evaluated.

In Japan, there are no drugs approved for marketing to treat COVID-19. Under the tense situation with the state of emergency declared by the government, and for the reasons listed below, allowing the use of remdesivir in Japan by Special Approval for Emergency has a certain level of significance, only if the precautions described in FACT SHEET FOR HEALTH CARE PROVIDERS are observed. (FACT SHEET was prepared upon the issuance of Emergency Use Authorization in the U.S.)

- An *in vitro* study and nonclinical studies using infected animal models have demonstrated the antiviral activity of remdesivir against SARS-CoV-2 [see Section 3.2].
- The preliminary results of the multiregional phase III placebo-controlled study (ACTT study) [see Section 2.1] in patients with COVID-19 have suggested the treatment effect of remdesivir against COVID-19.
- A certain level of tolerability of remdesivir has been suggested by clinical experience with remdesivir, including studies in healthy adults [see Section 3.1] and a study in patients with Ebola virus infection [see Section 3.1].
- The U.S. FDA has issued Emergency Use Authorization to permit the use of remdesivir.

There is extremely limited clinical experience with remdesivir currently, and the efficacy and safety data of remdesivir are expected to increase in the future. Therefore when the use of remdesivir is considered, the benefit-risk balance of remdesivir should be carefully evaluated also based on the latest information available at each time point of treatment. The applicant should take appropriate actions so that relevant information is easily accessible to healthcare professionals.

3.1 Emergency Use Authorization by U.S. FDA

The U.S. FDA evaluated the preliminary results of the multiregional phase III study (ACTT study [NCT04280705, see Section 2.1] and Study GS-US-540-5773 (NCT04292899, see Section 2.2), and concluded that the known and potential risks of remdesivir were acceptable relative to the known and potential efficacy of remdesivir in hospitalized patients with severe COVID-19 [32] [https://www.fda.gov/media/137564/download (as of May 5, 2020)]. The FACT SHEET FOR HEALTH

[32] The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product remdesivir for treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in adults and children hospitalized with severe disease. Severe disease is defined as patients with an oxygen saturation (SpO_2) ≤ 94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).

CARE PROVIDERS [https://www.fda.gov/media/137566/download (as of May 5, 2020)], which is prepared for a product given Emergency Use Authorization, contains the following information supporting the Emergency Use Authorization for remdesivir.

1) Compassionate use experience of remdesivir [see Section 2.3]

2) Foreign phase I studies in healthy adults (Studies GS-US-399-1812, GS-US-399-1954, GS-US-399-4231, and GS-US-399-5505)
   - Remdesivir was administered to 138 subjects. A temporary increase in AST and ALT was observed in once daily repeated administration.

3) A foreign phase II/III study in patients with Ebola virus infection (PALM study, *N Engl J Med.* 2019;381:2293-303, NCT03719586)
   - A randomized, open-label, parallel-group study
   - A total of 175 patients were randomized to the remdesivir group.
   - Nine patients in the remdesivir group experienced serious adverse events that were not considered due to the primary disease by the investigator of the study site or others. One of these serious adverse events was hypotension that occurred during the treatment with the starting dose (200 mg or 5 mg/kg) and led to cardiac arrest resulting in death. This event (hypotension) was considered to be causally related to remdesivir. The independent safety monitoring committee stated that it was hard to conclude whether the death was caused by the fulminant Ebola virus infection, the primary disease, or by remdesivir.

3.2 Efficacy

In an *in vitro* study using human primary-cultured airway epithelial cells, remdesivir showed an antiviral activity against a clinical isolate of SARS-CoV-2 (50% effective concentration [EC_{50}]: 9.9 nmol/L). In rhesus monkeys infected with SARS-CoV-2, remdesivir improved clinical signs of respiratory disease and decreased viral RNA load in the lung. Thus, remdesivir has been shown to be effective against SARS-CoV-2 non-clinically.

As for clinical studies, the preliminary results from the multiregional phase III study (Study GS-US-540-5773, NCT04292899) [see Section 2.2] cannot be fully interpreted because the study has no control (e.g., placebo) group. Whereas, in the placebo-controlled, multiregional phase III study (ACTT study, NCT04280705) [see Section 2.1], a preliminary analysis showed that the median time to recovery was 11 days in the remdesivir group versus 15 days in the placebo group (hazard ratio 1.31 [95% CI: 1.12, 1.54; $P < 0.001$]), and that mortality was 8.0% for the remdesivir group and 11.6% for the placebo group ($P = 0.059$). These results suggest the clinical efficacy of remdesivir. On the other hand, in a clinical study in China (NCT04257656, *Lancet*. 2020 Apr 29 https://doi.org/10.1016/S0140-6736(20)31022-

9)[33] conducted according to a placebo-controlled design as with the ACTT study, the median time (first quartile, third quartile) to clinical improvement[34] within 28 days after randomization was 21 [13.0, 28.0] days in the remdesivir group and 23 [15.0, 28.0] days in the placebo group, with a hazard ratio of 1.23 [95% CI: 0.87, 1.75]. According to the authors, since this study was prematurely terminated because of the failure to enroll the planned number of patients due to a change in the study environment, its results might not be enough for appropriately evaluating the usefulness of remdesivir. (*Lancet*. 2020 April 29 https://doi.org/10.1016/S0140-6736(20)31023-0)). In view of the above, no definite conclusion can be drawn regarding the effectiveness of remdesivir currently. More rigorous evaluation awaits the results of ongoing clinical studies. When new efficacy data become available from the ongoing or future clinical studies, etc., the applicant should promptly submit the data and provide healthcare professionals with information necessary for the proper use of remdesivir.

No *in vitro* studies have been conducted on the emergence of SARS-CoV-2 strains resistant to remdesivir. Also, no clinical data are available currently on the emergence of resistant SARS-CoV-2 strains with reduced susceptibility to remdesivir. On the other hand, in an *in vitro* study on resistance acquisition against remdesivir using mouse hepatitis virus, a rodent coronavirus, mutations were observed in the amino acids of RNA-dependent RNA polymerase, resulting in decreased susceptibility to remdesivir. This finding suggests the possibility that similar mutations may occur in the polymerase region of SARS-CoV-2, resulting in a change in the susceptibility to remdesivir. Since the presence or absence of resistance acquisition may provide important information on the efficacy of remdesivir, such information should be continuously collected from published reports as well as from studies after the market launch, and newly obtained information should be promptly provided to healthcare professionals.

3.3 Safety

The safety data of remdesivir is extremely limited, precluding a conclusion on the safety profiles of remdesivir, including those in the Japanese population. Healthcare professionals should be advised to follow the precautions described in FACT SHEET FOR HEALTH CARE PROVIDERS, which was prepared upon the issuance of Emergency Use Authorization. They should also be appropriately informed of the issues described in the following sections. The applicant should, after the market launch, continue to collect the safety data of remdesivir and provide newly obtained information to healthcare professionals promptly and appropriately.

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[33] The outline of the clinical study was as follows:
- Placebo-controlled, randomized, double-blind study in which 237 patients were assigned to the remdesivir group or placebo group at a 2:1 ratio.
- Main inclusion criteria: Patients aged ≥18 years, PCR positive for SARS-CoV-2, pneumonia (chest imaging, oxygen saturation ≤94% [on room air], or P/F ratio ≤300 mgHg), within 12 days after the onset of symptoms.
- Main exclusion criteria: Pregnancy, breast-feeding, hepatic cirrhosis, ALT or AST >5 times the upper limit of normal, eGFR <30 mL/min/1.73 m^2, renal replacement therapy, hemodialysis, peritoneal dialysis, anticipated transfer to another hospital within 72 hours.
- Dosage regimen: Remdesivir (200 mg) or placebo was administered intravenously on Day 1, followed by once-daily intravenous administration of remdesivir (100 mg) or placebo from Days 2 through 10.
- Others: Co-administration of lopinavir/ritonavir was permitted.

[34] Clinical improvement was defined as a ≥2-point improvement in the following 6-point ordinal scale, or live discharge from the hospital, whichever came first: (1) Discharged or having reached discharge criteria, (2) hospitalized but not requiring oxygen therapy, (3) hospitalized for oxygen therapy (but not requiring non-invasive ventilation or high-flow oxygen therapy), (4) hospitalized for non-invasive ventilation or high-flow oxygen therapy, (5) hospitalized for ECMO or invasive mechanical ventilation, and (6) death.

3.3.1 Administration to patients with liver disorder or hepatic impairment

In foreign phase I studies in healthy adults (Studies GS-US-399-1954[35] and GS-US-399-5505[36]), AST increase and ALT increase of Grade 1 and 2 occurred,[37] but resolved after treatment discontinuation. Table 9 shows Grade ≥3 liver function test abnormal observed in the multiregional phase III study (Study GS-US-540-5773). There were no events related to Grade ≥3 hepatic dysfunction.

Table 9. Grade ≥3 liver function test abnormal in multiregional phase III study (Study GS-US-540-5773)

		5-day treatment	10-day treatment	Total
ALT	Grade 3	8/194 (4)	11/191 (6)	19/385 (5)
	Grade 4	4/194 (2)	5/191 (3)	9/385 (2)
AST	Grade 3	11/194 (6)	7/190 (4)	18/384 (5)
	Grade 4	3/194 (2)	4/190 (2)	7/384 (2)
Total bilirubin	Grade 3	1/193 (1)	3/190 (2)	4/383 (1)
	Grade 4	0	1/190 (1)	1/383 (<1)

n/N (%)

In the foreign phase II/III study (PALM study, NCT03719586) in patients with Ebola virus infection, neither serious liver function test abnormal nor hepatic function-related events were reported in 175 patients who had been assigned to the remdesivir group.

In the compassionate use experience of remdesivir [see Section 2.3], liver function test abnormal was reported in 11.7% (19 of 163) of patients. The time to occurrence of the abnormality from the initial dose of remdesivir was 1 to 16 days. Of the 19 patients, 4 discontinued remdesivir due to liver function test abnormal on Day 5 after the start of treatment according to the pre-specified rule. Serious hepatic dysfunction-related events were reported in 7 patients. Serious blood bilirubin increased was reported in seriously ill patients with septic shock or multiorgan failure. Hyperbilirubinaemia or other adverse events suggestive of hepatic dysfunction were not reported in other patients.

The exclusion criteria for clinical studies include patients with AST or ALT >5 times the upper limit of normal.

Thus, remdesivir may cause liver disorder. In light of these observations, physicians should be advised to use caution in administering remdesivir to patients with liver disorder or hepatic impairment.

3.3.2 Administration to patients with renal disorder or renal impairment

Repeated administration of remdesivir to rats and rhesus monkeys caused degeneration/necrosis of renal tubules at dose levels below clinical exposure, whereas no such findings were observed in cynomolgus monkeys after repeated administration. In clinical studies in healthy adults (a clinical study administering up to 225 mg remdesivir intravenously in a single dose, a clinical study administering 150 mg remdesivir intravenously once daily for up to 14 days, and other studies), no kidney-related adverse events were reported. With only scarce safety data in humans available clinically, whether the renal toxicity observed in rats is relevant to humans is unclear. In compassionate use of remdesivir, renal disorders such as renal dysfunction, acute renal disorder, and renal failure were reported despite the

35) Remdesivir (150 mg) was administered once daily for 7 or 14 days.
36) Remdesivir (200 mg) was administered on Day 1, followed by once-daily administration of 100 mg from Days 2 through 5 or Days 2 through 10.
37) ALT increased up to 10 times the baseline value in a patient without hepatic impairment as a comorbidity.

renal function-related exclusion criteria, and resulted in treatment discontinuation in some of these patients. Thus, remdesivir treatment may cause serious renal disorders. Also, excipient sulfobutylether-β-cyclodextrin sodium (SBECD) is toxic to renal tubules, and its safety is not established in patients with reduced renal function. In light of these observations, physicians should be advised to use caution in administering remdesivir to patients with renal disorder or renal impairment.

3.3.3 Administration to children

Nonclinical studies did not reveal any finding of concern unique to children. However, whether to administer remdesivir to a child should be determined after comparing the benefits and risks of remdesivir, for the following reasons: (1) Renal function is immature in children, and renal toxicity is observed in nonclinical studies [see Section 3.3.2], (2) renal safety of excipient SBECD in children aged <2 years has not been established, and (3) no clinical study in children has been conducted. Remdesivir administration to children should be done carefully while systemic conditions, including renal function, are closely monitored.

3.3.4 Administration to pregnant or breast-feeding women

Nonclinical studies did not detect toxicity related to fetal development or neonatal physical development. However, remdesivir therapy in pregnant women or possibly pregnant women should be considered only when the expected therapeutic benefits outweigh the possible risks associated with treatment, for the following reasons: (1) Pregnant women were excluded from the compassionate use of remdesivir,[38)] and (2) no clinical studies have investigated the safety of remdesivir in pregnant women. A study of fertility and early embryonal development in rats revealed the effect of remdesivir on the number of corpus luteum and live embryo. This information should be included in the package insert for precaution.

Nonclinical studies showed transfer of remdesivir to pups through maternal milk, but no findings suggestive of safety problems were observed in pups. Nevertheless, remdesivir administration to breast-feeding women should be considered only when the expected therapeutic benefits outweigh the possible risks associated with treatment because no clinical data are available on breast-feeding women or infants.

3.3.5 Others

3.3.5.1 Other adverse events

The following adverse events were reported in patients receiving remdesivir. This information should be provided appropriately to healthcare professionals.

Dizziness, pruritus generalized, infusion site extravasation, medical device site dermatitis, ecchymosis, presyncope, medical device site irritation, lipase increased (Grade 3), amylase high (Grade 1), cholesterol total increased (Grade ≤2), low-density lipoprotein (LDL) cholesterol increased (Grade ≤2), constipation, dyspepsia, pain in extremity, headache, nausea, vomiting, tremor, decreased appetite, ALT increased (Grade ≤2), AST increased (Grade ≤2), diarrhoea, dermatitis contact, pruritus, infusion site haemorrhage, infusion site pain, electrocardiogram T wave inversion (Grade 1), PT prolongation (Grade

38) The applicant explained that the target patients to be treated with compassionate-use remdesivir were changed to include pregnant women and children on [redacted], 2000. Compassionate-use remdesivir was administered to 76 children aged <18 years and 96 pregnant women (FACT SHEET FOR HEALTH CARE PROVIDERS).

1), hyperglycaemia, erythema, rhinorrhoea, serum calcium (Grade 1), potassium increased (Grade 1), and hypotension.[39)]

3.3.5.2 Monitoring

Only limited safety data on remdesivir are available currently. In order to detect adverse events as early as possible, it is essential to monitor clinical symptoms and laboratory data (white blood cell count, differential white blood count, hemoglobin, hematocrit, platelet count, creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase (ALP), prothrombin time, etc.) every day during the treatment with remdesivir.

3.4 Actions to be taken after market launch

Since there are only extremely limited data on the quality, efficacy, and safety of remdesivir, particularly on the efficacy and safety in Japanese patients, the following actions should be taken appropriately.

- The applicant is required to establish a system that enables prompt collection and evaluation of the efficacy and safety data of remdesivir. When learning about diseases, disorders, or death caused by remdesivir or other causes, the applicant is required to report them promptly. In particular, information on matters that are required to be reported within the period specified by Article 228-20, Paragraph 1, Item (1) of the Ministerial Ordinance for Enforcement of Pharmaceuticals and Medical Devices Act should be submitted at the earliest convenience, notwithstanding the provisions of the paragraph.
- Extremely limited data are now available on the efficacy and safety of remdesivir. As soon as results of the ongoing clinical trials and clinical studies are obtained, they should be promptly reported and published in a compiled form.
- After the market launch, the applicant is required to promptly collect the efficacy and safety data of remdesivir (e.g., adverse drug reaction information) from all patients treated with remdesivir, wherever possible, until data are gathered from a certain number of patients, and to take necessary actions to ensure the proper use of remdesivir.
- The applicant is required to take actions so that the updated efficacy and safety information on remdesivir is easily accessible to healthcare professionals.
- After the completion of the Early Post-marketing Phase Vigilance, the applicant is required to continue to conduct pharmacovigilance activities and risk minimization activities similar to the Early Post-marketing Phase Vigilance, until safety evaluation of remdesivir in Japan is completed to a sufficient extent.
- The applicant is required to take necessary actions to ensure that healthcare professionals and patients (or their legally acceptable representatives) who use remdesivir are informed and understand that remdesivir has been granted Special Approval for Emergency and the objectives of said approval.
- The applicant is required to request that physicians administer remdesivir only to patients considered eligible for treatment with remdesivir who, or whose legally acceptable representatives, have been provided with the efficacy and safety information of remdesivir in written form, and who have provided written informed consent before the treatment.
- The applicant is required to collect information on the investigator-initiated clinical trial (ACTT study, NCT04280705) as well and evaluate its data and take other appropriate actions.

[39)] Hypotension resulting in fatal cardiac arrest was reported in a patient with Ebola virus infection after remdesivir administration.

3.5 Indication and dosage and administration

Remdesivir should be granted Special Approval for Emergency only with the approval conditions listed below. The indication and dosage and administration should be determined based on the contents of FACT SHEET FOR HEALTH CARE PROVIDERS prepared for the Emergency Use Authorization by the U.S. FDA, as shown below. The only dosage investigated was that used in clinical studies of remdesivir in adult patients with COVID-19. Remdesivir should be used within the range of said dosage. It should be kept in mind that the optimal dosage for remdesivir may be determined based on the information to be obtained in the future. The dosage and administration in children have been determined based on the plasma remdesivir concentration over time in children predicted by modeling and simulation, and the model includes the age group with no available clinical data on remdesivir. Whether to administer remdesivir to a child should be judged by comparing the benefits and risks based on the latest information.

Indication

Disease caused by SARS-CoV-2 infection (COVID-19)

Dosage and Administration

The usual dosage for adults and children weighing ≥40 kg is 200 mg of remdesivir infused intravenously on Day 1, followed by once-daily intravenous infusion of 100 mg from Day 2 onward.

The usual dosage for children weighing ≥3.5 kg and <40 kg is 5 mg/kg of remdesivir infused intravenously on Day 1, followed by once-daily intravenous infusion of 2.5 mg/kg from Day 2 onward.

The total duration of remdesivir therapy is ≤10 days.

Approval Conditions and Other Requirements

1) The applicant is obliged to fulfill the following duties set forth in each item of Article 28 of the Cabinet Order for Enforcement of the Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 2 of the Pharmaceuticals and Medical Devices Act.
   (1) Matters related to Item (1)
   Extremely limited data are now available on the efficacy and safety of the product. As soon as results of the ongoing clinical trials and clinical studies are obtained, they should be promptly reported in a compiled form.
   (2) Matters related to Item (2)
   When learning about diseases, disorders, or death suspected to be caused by the product or other causes, the applicant is required to report them promptly.
   (3) Matters related to Item (3)
   The applicant is required to take necessary actions to ensure that healthcare professionals and patients (or their legally acceptable representatives) who use the product are informed and understand that the product has been granted Special Approval for Emergency and the objectives of said approval.

(4) Matters related to Item (4)

The applicant is required to report the parties to whom the product has been sold or provided and the quantity sold or provided per party.

2) The product is approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:

(1) The applicant is required to develop and appropriately implement a risk management plan.

(2) The product is granted Special Approval for Emergency, in accordance with the provision in Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. There is extremely limited clinical experience with the product. Therefore, after the market launch, the applicant is required to promptly collect the efficacy and safety data of the product (e.g., adverse drug reaction information) from all patients treated with the product, wherever possible, until data are gathered from a certain number of patients, and to take necessary actions to ensure the proper use of the product. The applicant is also required to periodically report the information obtained.

(3) The applicant is required to take actions necessary for the proper use of the product, based on the results of an additional safety assessment of the product.

(4) The applicant is required to take actions so that the updated efficacy and safety information on the product is easily accessible to healthcare professionals.

(5) The applicant is required to request that physicians administer the product only to patients considered eligible for treatment with the product who, or whose legally acceptable representatives, have been provided with the efficacy and safety information of the product in written form, and who have provided written informed consent before the treatment.

(6) Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act (Ministry of Health and Welfare [MHW] Ordinance No.1 of 1961), the grace period for data submission is 9 months after the approval. The applicant is required to submit results of the currently ongoing clinical studies at the earliest convenience when they become available. The applicant is also required to submit other data to Pharmaceuticals and Medical Devices Agency (PMDA) at the latest within 9 months after the approval. If newly submitted data, etc., necessitate any change in the approved product information, a change in the approved product information may be ordered in accordance with the provision in Article 74-2, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

3) The product is approved based on Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. The approval may be withdrawn in accordance with the provision in Article 75-3 of the Act in a case where (1) the product does not conform to any Item of Article 14-3, Paragraph 1 of the Act or (2) the withdrawal is necessary to prevent the emergence or expansion of public health risks.

Appendix

List of Abbreviations

ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
Cabinet Order for Enforcement of Pharmaceuticals and Medical Devices Act	Cabinet Order for Enforcement of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Cabinet Order No. 11 of 1961)
EC_{50}	50% effective concentration
ECMO	Extracorporeal membrane oxygenation
FDA	Food and Drug Administration
LDL	Low-density lipoprotein
MERS	Middle East respiratory syndrome
Ministerial Ordinance for Enforcement of Pharmaceuticals and Medical Devices Act	Ministerial Ordinance for Enforcement of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Ordinance of the Ministry of Health and Welfare No. 1 of 1961)
PCR	Polymerase chain reaction
Pharmaceuticals and Medical Devices Act	Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Act No. 145 of 1960 [August 10, 1960])
PMDA	Pharmaceuticals and Medical Devices Agency
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBECD	Sulfobutylether-β-cyclodextrin sodium
WHO	World Health Organization
Wuhan	Wuhan City, Hubei Province, China