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To: Commissioners of Prefectural/Cities with Established Health Centers/Special District Health Department (Bureau)

Director of the Pharmaceutical Evaluation Division, PSEHB, MHLW
(Official seal omitted)

Director of the Pharmaceutical Safety Division, PSEHB, MHLW
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Points to Consider for Use of Remdesivir

Remdesivir (brand name: Veklury for Intravenous Injection 100 mg (Solution), Veklury for Intravenous Injection100 mg (Lyophilized powder)) (hereinafter referred to as “remdesivir”) has been given Special Approval for Emergency today for its indication of SARS-CoV-2 infection”.

Special Approval for Emergency refers to a system where a pharmaceutical product is exceptionally given approval as a drug that needs to be used urgently for the purpose of preventing the spread of disease or other health hazards that may have significant impact on the life and health of the people under provisions of Article 14-3, Paragraph 1 in the Act on Securing Quality, Efficacy, and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960) (Hereinafter referred to as “Pharmaceuticals and Medical Devices Act”). Although remdesivir is approved because it is expected to be effective against new coronavirus infection, limited results have been obtained from its clinical studies. Therefore, medical institutions and physicians using remdesivir are requested to pay special attention to its use especially until sufficient data are collected regarding treatment with remdesivir.

Please inform medical institutions under your jurisdiction of the following matters as specific points to consider when using remdesivir. In addition, please inform the wholesalers under your jurisdiction to handle it appropriately.

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Note

1. Positioning of remdesivir

Remdesivir is granted Special Approval for Emergency under the provisions of Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act as shown below. Therefore, the procedures are different from those for approval under Article 14, Paragraph 1 of the Act. Please pay special attention and consideration when handling remdesivir.

Article 14-3: If an item that an applicant for approval prescribed in Article 14 intends to market falls under both of the following items as pharmaceuticals specified by Cabinet Order, the Minister of Health, Labour and Welfare may, notwithstanding of the provisions of paragraphs (2), (5), (6) and (8) of the same Article, grant approval for such item prescribed in the same Article after obtaining opinions from the Pharmaceutical Affairs and Food Sanitation Council:

(1) Pharmaceuticals that needs to be used urgently for the purpose of preventing the spread of disease or other health hazards that may have significant impact on the life and health of the people, and for which no proper method is available other than the use of such pharmaceuticals;

(2) With respect to use, pharmaceuticals that are authorized to be sold, provided, or stored or displayed for the purpose of sale or provision thereof in foreign countries (limited to countries specified by Cabinet Order as those having a marketing approval system or other systems recognized as being of an equivalent level to that of Japan in terms of quality, efficacy, and safety to be secured for the pharmaceuticals).

2. Approval Conditions, etc.

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 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.

3. Indications of remdesivir

The “infection caused by SARS-CoV-2” in the indication of remdesivir refers only to “the one whose pathogen is coronavirus of the genus Betacoronavirus (limited to what was newly reported from the People's Republic of China to the World Health Organization in January 2020 as the one whose pathogen has the ability to transmit to humans).”

4. Proper use of remdesivir

(1) Data on the optimal dosage and administration have not been obtained at the time of approval. Therefore, the recommended optimal dosage and administration may be changed based on the results of ongoing clinical trials and clinical studies.

(2) The Precautions concerning Patients with Specific Backgrounds in the package insert of remdesivir states that it is desirable not to administer remdesivir to patients with hepatic dysfunction with ALT level ≥5 times of upper limit of normal (ULN). In patients with renal impairment, treatment with remdesivir may exacerbate renal impairment. In particular, the package insert states that remdesivir should be used to patients with severe renal impairment only when the therapeutic benefit outweighs the risks. A decision on treatment with remdesivir should be made based on the statements. Refer to the package insert for other precautions.

(3) The Important Precautions for remdesivir include the following statements that “Since acute renal disorder and hepatic function disorder may occur, renal and hepatic function tests should be performed every day before and during treatment and the patient's condition should be carefully monitored”. Therefore, clinical symptoms and laboratory test values must be appropriately monitored for early detection of adverse events. In ongoing clinical studies, measurement of following items is specified as safety laboratory tests: white blood cell count, differential white blood count, haemoglobin, haematocrit, platelet count, creatinine, glucose, bilirubin

total, AST, ALT, and prothrombin time. Please refer to them in treatment with remdesivir. Since remdesivir may affect the kidney, urine analysis should be performed as necessary.

(4) When selecting applicable patients, please refer to the following points, in particular, in the eligibility and exclusion criteria used at the time of compassionate use which are included in the application document of remdesivir.

< Eligibility criteria >

- Positive PCR result for SARS-CoV-2
- Oxygen saturation of ≤94%, oxygen inhalation or NEWS 2 score of ≥4
- Being hospitalized

< Exclusion criteria >

- Patients with symptoms of multi-organ failure
- Patients requiring continuous vasopressors
- ALT >5 times × ULN
- Patients with creatinine clearance <30 mL/min or on dialysis
- Pregnant women

5. Request for cooperation in all-case surveillance, etc., of remdesivir

All cases, or as many applicable cases as possible, need to be surveyed as a condition for approval of remdesivir. Since it is necessary to collect data on safety and efficacy of remdesivir especially promptly, the medical institutions using remdesivir are requested to cooperate in providing data promptly.

Moreover, if any suspicious symptom is observed as an adverse reaction and its reporting is considered necessary, please report it to PMDA based on the Pharmaceuticals and Medical Devices Safety Information Reporting System so that useful information on remdesivir will be accumulated.