ANNEX I

CONDITIONS OF USE, CONDITIONS FOR DISTRIBUTION AND PATIENTS TARGETED ADRESSED TO MEMBER STATES

REMDESIVIR GILEAD

1. MEDICINAL PRODUCT FOR COMPASSIONATE USE

- **Name of the medicinal product for Compassionate Use: REMDESIVIR GILEAD**
- **Active substance(s): Remdesivir (RDV)**
- **Pharmaceutical form:**
  - **Powder for concentrate for solution for infusion (100 mg),**
  - **Concentrate for solution for infusion (100 mg)**
- **Route of administration: IV**
- **Strength: see above**

2. NAME AND CONTACT DETAILS OF THE COMPANY

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3. TARGET POPULATION

For the treatment of adult and paediatric patients from 12 year of age weighing at least 40 kg with severe COVID-19 (hospitalization requiring supplemental oxygen, non-invasive ventilation, high-flow oxygen devices, invasive mechanical ventilation, or ECMO), confirmed by Polymerase chain reaction (PCR) or who have known contact with a confirmed case of COVID-19, with PCR pending.

4. CONDITIONS FOR DISTRIBUTION

Medicinal product subject to restricted medical prescription.

Treatment should be initiated in hospital setting only.

5. CONDITIONS OF USE

5.1 Posology

- **Dosing recommendations including any specificity linked to the initiation of treatment**

The recommended dosage of Remdesivir in patients 12 years of age and older and weighing at least 40 kg requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) is a single loading dose of 200 mg on Day 1 followed by once-daily maintenance doses of 100 mg for 9 days.

The recommended dosage of Remdesivir in patients 12 years of age and older and weighing at least 40 kg not requiring invasive mechanical ventilation and/or ECMO is a single loading dose of 200 mg on Day 1 followed by once-daily maintenance doses of 100 mg for 4 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e., up to a total of 10 days).

Remdesivir is to be administered via IV infusion in a total volume of up to 250 mL of 0.9% saline over 30 minutes. The infusion time may be extended up to 120 minutes.

- **Treatment duration and monitoring**

It is recommended that regular laboratory assessments, including hepatic function tests, be performed in subjects receiving remdesivir in order to monitor hepatic function. For subjects with an ALT > 5 x upper limit of normal (ULN) permanent discontinuation of remdesivir treatment should be considered. Any observed liver function-related laboratory abnormalities or possibly related AEs should be treated appropriately and followed to resolution.

Measurement of eGFR should be performed while subjects are receiving remdesivir, particularly subjects with known renal impairment at the start of therapy. For subjects with an eGFR of < 30%,

permanent discontinuation of remdesivir treatment should be considered. Subjects should then be followed as clinically indicated until eGFR returns to baseline or is otherwise explained, whichever occurs first.

- **Specific populations**

Renal impairment
No dose adjustment of remdesivir is required for patients with mild and moderate renal impairment. Patients with renal failure (eGRF < 30 mL/min) or dialysis or continuous Veno-Venous Hemofiltration must not receive remdesivir.

Hepatic impairment
No dose adjustment of remdesivir is required for patients with mild and moderate hepatic impairment.
Patients with hepatic impairment (ALT > 5 x upper limit of normal (ULN)) must not receive remdesivir.

Elderly
No dose adjustment of remdesivir is required for elderly patients.

Paediatric population

The safety and efficacy of remdesivir in children below 12 years have not yet been established. No data available.

- **Method of administration**

Intravenous use

Remdesivir should be administered as an intravenous infusion administered over a 30 to 120 minutes period.

If an anaphylactic reaction occurs, the infusion should be discontinued, appropriate medical therapies should be administered and treatment with remdesivir should be discontinued.

- **Preparation of the medicinal product to be administered**

Detailed information regarding drug administration, reconstitution and dilution instructions are provided in a pharmacy manual provided to the investigators.

Powder for concentrate for solution for infusion 100 mg:
- Reconstitute with 19 ml of water for injection (100 mg). After reconstitution, each vial contains a 5 mg/mL remdesivir concentrated solution with sufficient volume to allow withdrawal of 20 ml (100 mg remdesivir).
- Dilute the reconstituted powder (i.e concentrated solution) in intravenous fluids up to 250 mL prior to intravenous administration.
- Diluents that may be used: 0.9 % (9 mg/ml) sodium chloride in water (saline) or 5 % (50 mg/ml) glucose (dextrose) in water.
- The diluted solutions should be used immediately, please refer to section 5.8.

Concentrate for solution for infusion 100 mg (5 mg/ml):
- Allow frozen vial to thaw before dilution.
- Dilute thawed concentrated solution in intravenous fluids up to 250 mL prior to intravenous administration.
- Diluents that may be used: 0.9 % (9 mg/ml) sodium chloride in water (saline) or 5 % (50 mg/ml) glucose (dextrose) in water.
- The diluted solutions should be used immediately, please refer to section 5.8.

5.2 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients
- Evidence of multiorgan failure

- The use of more than one pressor for septic shock (the use of 1 pressor at low/medium doses for inotropic support due to the use of sedation and paralytics while on the ventilator is allowed)
- ALT > 5 x upper limit of normal (ULN) by local laboratory measure
- Renal failure (eGRF < 30 mL/min) or dialysis or continuous Veno-Venous Hemofiltration
- Participation in any other clinical trial of an experimental agent treatment for COVID-19

5.3 Special warnings and precautions for use

In clinical studies, transient elevations in ALT and AST have been observed with single doses of remdesivir up to 225 mg and multiple once-daily doses of remdesivir 150 mg for up to 14 days, with mild, reversible PT prolongation in some subjects but without any clinically relevant change in INR or other evidence of hepatic effects. The mechanism of these elevations is currently unknown.

In nonclinical animal studies, toxicity findings were consistent with dose-dependent and reversible kidney injury and dysfunction. In clinical studies, no evidence of nephrotoxicity has been observed with single doses of remdesivir up to 225 mg or multiple once-daily doses of remdesivir 150 mg for up to 14 days.

5.4 Interaction with other medicinal products and other forms of interaction

No clinical drug-drug interaction studies have been conducted with remdesivir.

There are no available data on potential interactions between remdesivir and other anti-COVID-19 investigational agents.

Remdesivir should not be used with other drugs that have significant hepatotoxicity.

5.5 Pregnancy and lactation

Pregnancy and contraception requirements
There are no data from the use of remdesivir in pregnant women. The use of remdesivir in pregnant woman is not recommended.

Breast-feeding
It is unknown whether remdesivir/metabolites are excreted in human milk.

Fertility
No human data on the effect of remsidivir on fertility are available.

5.6 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 5.1.

5.7 Overdose

There is no known antidote for remdesivir. In the case of overdose, the subject should receive standard treatment for overdose and supportive therapy based on the subject's signs and symptoms.

5.8 Shelf life

Powder for concentrate for solution for infusion

51 months

Concentrate for solution for infusion

48 months

Powder for concentrate for solution for infusion and Concentrate for solution for infusion:

Chemical and physical in-use stability has been demonstrated for 24 hours at 25 °C.
From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

5.9 Storage conditions

Powder for concentrate for solution for infusion

Store below 30 °C.

Concentrate for solution for infusion

Store in a freezer (−25 °C to −10 °C). Repeated freezing and thawing is not allowed.

5.10 Special precautions for disposal

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6. OTHER INFORMATION

- **Summary of relevant pharmacological properties**

Mechanism of action
Remdesivir has been designed to efficiently deliver the monophosphate nucleoside analog GS-441524 into cells. Inside cells, the GS-441524 monophosphate undergoes rapid conversion to the pharmacologically active nucleoside triphosphate form GS-443902. Efficient metabolism of remdesivir and/or the diastereomeric mixture GS-466547 to the nucleoside triphosphate GS-443902 has been demonstrated in multiple cell types.

Antiviral activity in cell culture
Empirical nonclinical data on antiviral activity of remdesivir on SARS-CoV-2 is currently limited to a few *in vitro* observations and is mainly extrapolated from *in vitro* and *in vivo* studies with other Coronavirus types (i.e. SARS CoV and MERS-CoV), that are presumed to have similar pathogenesis and viral susceptibility as does Covid-19 and SAR-Cov2. These studies indicate that prophylactic treatment is more effective than when RDV is given after viral challenge. Furthermore, there are no data on the initiation of treatment more than one day after challenge.

- **Summary of relevant Clinical properties**

Clinical efficacy

Clinical Trials in Subjects with COVID-19:

NIAID ACTT-1 Study

A randomized, double-blind, placebo-control clinical study evaluated remdesivir 200 mg once daily for 1 day followed by remdesivir 100 mg once daily for 9 days (for a total of up to 10 days of intravenously administered therapy) in hospitalized adult patients with COVID-19. Patients in this study could have either mild-to-moderate or severe COVID-19. Severe disease was defined as hospitalization requiring supplemental oxygen, non-invasive ventilation, high-flow oxygen devices, invasive mechanical ventilation, or ECMO. The trial enrolled 1063 hospitalized patients in a 1:1 manner to receive remdesivir or placebo. The primary clinical endpoint was time to recovery until Day 29 after randomization. [Section will be updated once the data had been published].

Clinical safety
The safety profile of remdesivir is incompletely characterised. Hepatotoxicity is an identified risk.

7. CONDITIONS FOR SAFETY MONITORING

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and Responsibilities defined in Article 28(1) and 28(2) of said Regulation are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. Therefore, the company and the Member States shall ensure that these pharmacovigilance rules and responsibilities are fulfilled.

The company shall submit every 6 months a periodic safety update report.

In addition, the company shall submit to EMA monthly expedited summary safety reports, following the format described in the CHMP Opinion.

8. DATE OF CHMP OPINION

11/05/2020

Information on compassionate use are available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu.