EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

03 April 2020
EMA/178637/2020 – Rev.2*
Human Medicines Division

Summary on compassionate use

Remdesivir Gilead

International Non-proprietary Name: remdesivir

Procedure No. EMEA/H/K/005622/CU

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

*This document has been re-published to include data that were initially redacted while waiting for their publication (see p.42-44).

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1 Background information on the procedure

1.1 Submission of the dossier

Estonia, Greece, The Netherlands and Romania on 25 and 26 March 2020 requested from the Agency (EMA) a CHMP opinion on the compassionate use for the above-mentioned medicinal product in accordance with Article 83(3) of Regulation (EC) No 726/2004.

The legal basis for this application refers to:

Article 83(3) of Regulation (EC) No 726/2004

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Dr Janet König (DE), Multinational Team with AT (Quality)

Co-Rapporteur: Dr Filip Josephson (SE)

1.2 Steps taken for the assessment of the product

- The dossier was received by the EMA on 27 March 2020.
- The Applicant responded on 31 March 2020 and 01 April 2020 to questions raised by the Rapporteurs.
- The Rapporteur's Joint Assessment Report was circulated to all CHMP members and the company on 01 April 2020
- The procedure was discussed in an extraordinary CHMP meeting on 2 April 2020
- The opinion was adopted on 02 April 2020

2 General conditions for the manufacturer

2.1 Manufacturers

Manufacturers responsible for import and batch release in the European Economic Area

Both dosage forms:

Facility	Function
Fisher Clinical Services GmbH Im Woerth 3 Weil am Rhein, 79576 Germany	Importation and labeling
Fisher Clinical Services UK Limited Langhurstwood Road Horsham RH12 4QD United Kingdom	Importation and labeling
Gilead Sciences Ireland UC IDA Business and Technology Park Carrigtohill, Co. Cork Ireland	Importation, testing and QP release

Conclusion:

The applicant confirms that the manufacturing steps conducted at each facility are in full compliance with current Good Manufacturing Practices (cGMP) guidelines. Additionally, appropriate GMP certificates for the manufacturing / importation / batch release sites could be found at EudraGMPDP database.

2.2 Conditions of distribution

Medicinal product subject to restricted medical prescription. Treatment should be initiated in hospital setting only.

The company has stated in their submission that clinical trials are being prioritized to evaluate safety and efficacy for the treatment of COVID-19. CHMP supports this position and considers that the compassionate use programmes should be used for patients for which it is not possible to participate in a clinical trial. In light of the pandemic situation CHMP also considers that it is important to have the product made available to interested EU Member States in a fair and transparent manner.

2.3 Conditions for update of Compassionate Use to be implemented by the company

In accordance with Article 83(4) of Regulation (EC) No 726/2004, any change or new data having an impact on the CHMP compassionate use opinion as adopted by the CHMP, related to the conditions of use, distribution and targeted population of product, shall be communicated to the Agency (EMA) in order to update the CHMP Compassionate Use opinion as appropriate.

2.4 Conditions for safety monitoring to be implemented by the company

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

2.5 Conditions for safety monitoring to be implemented by the Member States.

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and Responsibilities defined in Article 28(1) and (2) of the Regulation (EC) No 726/2004 referring to centrally authorised medicinal products as defined in articles 3(1) and (2) are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. Therefore, the Member States shall ensure that these pharmacovigilance rules and responsibilities are fulfilled.

3 Scientific discussion

3.1 Introduction

As requested by the CHMP, the company submitted a dossier to support the compassionate use of the product.

Remdesivir when used as part of a compassionate use programme, is indicated for the treatment of adults with coronavirus disease 2019 (COVID-19) who require invasive mechanical ventilation.

Inclusion Criteria

- Willing and able to provide written informed consent, or with a legal representative who can provide informed consent, or enrolled under ICH E6(R2) 4.8.15 emergency use provisions as deemed necessary by the investigator (participants ≥ 18 years of age)
- Age ≥ 12 years
- Hospitalized with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) by Polymerase chain reaction (PCR) or known contact of confirmed case with syndrome consistent with COVID-19 with PCR pending
- Requiring invasive mechanical ventilation (e.g., via endotracheal intubation or tracheostomy)
- Adequate renal function with estimated glomerular filtration rate ≥ 30 ml/min by local laboratory measure
- ALT ≤ 5 x upper limit of normal (ULN) by local laboratory measure

Exclusion Criteria

- 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

Background

SARS-CoV-2 was identified as the cause of an outbreak of respiratory illness (COVID-19) that was first detected in Wuhan, China, in December 2019. The virus causes respiratory illness in people and can spread from person to person {Center for Disease Control (CDC) 2020, Center for Disease Control and Prevention (CDC) 2020}. Common signs of infection include fever, cough, shortness of breath, breathing difficulties, and other respiratory symptoms. In severe cases, SARS-CoV-2 can cause pneumonia, severe acute respiratory syndrome, kidney failure, and death {World Health Organization (WHO) 2020a}. On 30 January 2020, the International Health Regulations Emergency Committee of the WHO declared the COVID-19 outbreak a Public Health Emergency of International Concern {World Health Organization (WHO) 2020c}. Further to the WHO declaration, on 31 January 2020, Health and Human Services declared a public health emergency in the United States (US) {U. S. Department of Health & Human Services (DHHS) 2020}.

There are currently no approved effective therapeutic agents available for the treatment of COVID-19. The availability of a potentially effective antiviral agent with a favorable benefit/risk profile would address a serious unmet medical need for the treatment of patients with COVID-19. Remdesivir (GS-5734) is a single diastereomer monophosphoramidate prodrug of a nucleoside analog that is intracellularly metabolized into an analog of adenosine triphosphate that inhibits viral RNA polymerases and has broad spectrum activity against members of the filoviruses (eg, EBOV, MARV), CoVs (eg, SARS-CoV, MERS-CoV), and paramyxoviruses (eg, respiratory syncytial virus [RSV], Nipah virus [NiV], and Hendra virus).

There are several ongoing or planned studies on the clinical efficacy and safety of remdesivir for the treatment of COVID-19. (Table 1)

Table 1. Ongoing or planned studies on the clinical efficacy and safety of remdesivir for the treatment of COVID-19

Study Number	Study Title	Study Status
GS-US-540-5773 (SIMPLE)	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19	Ongoing
GS-US-540-5774 (SIMPLE)	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Moderate COVID-19 Compared to Standard of Care Treatment	Ongoing
IN-US-540-5755	Individual Patient Use Protocol for Wuhan Coronavirus	Ongoing
CO-US-540-5764	A Phase 3 Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult Patients With Mild and Moderate 2019-nCoV Respiratory Disease	Ongoing
CO-US-540-5776 (NIAID)	A Multicenter, Adaptive, Randomized Blinded Controlled Trial on the Safety and Efficacy Study of Investigational Therapeutics for the Treatment of 2019-nCoV	Ongoing
CO-US-540-5758	A Phase 3 Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir Combined with Standard of Care (SOC) in Hospitalized Adult Patients with Severe 2019-nCoV Respiratory Disease	Planned
CO-US-540-5804	Multi-centre, adaptive, randomized trial of the safety and efficacy of treatments of COVID-19 in hospitalized adults	Planned
GS-US-540-5821	Expanded Access Treatment Protocol: Remdesivir (RDV; GS-5734) for the Treatment of SARS-CoV2 (CoV) Infection	Planned
CO-US-540-5824 (WHO)	Multi-centre, adaptive, randomized trial of the safety and efficacy of treatments of COVID-19 in hospitalized adults	Planned

There is an ongoing single-patient compassionate use programme conducted both in the EU and outside the EU (Study IN-US-540-5755).

Remdesivir is currently not approved for marketing in any country.

3.2 Quality aspects

Introduction

Remdesivir is a single stereoisomer monophosphoramidate prodrug of a nucleoside analog that is being developed for the treatment of coronavirus (CoV) disease.

Remdesivir for compassionate use is provided in two dosage forms, a solution formulation and a lyophilized formulation. The standard term "Concentrate for solution for infusion" will be used in this document for the solution formulation, and the standard term "Powder for concentrate for solution for infusion" will be used for the lyophilized formulation.

The concentrate for solution for infusion is supplied as a sterile, preservative-free, clear, colourless to yellow, aqueous-based concentrated solution containing 5 mg/mL remdesivir to be diluted into infusion fluids prior to IV administration (see Annex I, 5.1 Preparation of the medicinal product to be administered).

The powder for concentrate for solution for infusion is a preservative-free, white to off-white to yellow, lyophilized solid containing 100 remdesivir to be reconstituted with sterile water for injection and diluted into IV infusion fluids prior to IV administration (see Annex I, 5.1 Preparation of the medicinal product to be administered).

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

Drug Substance

The chemical name for remdesivir is 2-Ethylbutyl (2S)-2-{[(S)-{[(2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl] methoxy}(phenoxy)phosphoryl]amino}propanoate. The molecular formula is $C_{27}H_{35}N_6O_8P$ and the molecular weight is 602,6 g/mol.

Remdesivir is a white to off-white or yellow non hygroscopic solid, practically insoluble in water and soluble in ethanol. Remdesivir has six chiral centres and is produced as a single stereoisomer. Different polymorphic forms exist and the active substance is manufactured as Form II or mixtures of Form II and another crystalline form. The mixture of forms and Form II show similar solubility and do not result in differences in finished product performance. The active substance is dissolved before final I.V. administration.

The active substance has been appropriately characterised by a range of analytical techniques.

The chemical synthesis was briefly described. The starting materials are relatively complex and only one synthetic step followed by deprotection and crystallisation is presented. The level of detail is brief, although some information on solvents used in previous steps and no use of class I solvents or intentionally added elements is stated. In total, the information on the manufacturing process is considered sufficient for use of the active substance in clinical trials and compassionate use programs. It is expected that this section is further extended for any upcoming applications.

Impurities have been evaluated and proposed structures for five impurities present in the remdesivir active substance are presented. One of the impurities, which is the diastereomer of remdesivir, is controlled as a specified impurity in the active substance specification.

A short discussion regarding assessment of mutagenic and potentially mutagenic impurities is presented and is acceptable considering the acute, potentially life-saving use. It is expected that this section is further extended for any upcoming applications.