

## REMDESIVIR SAFETY PROFILE

Date : 09-03-2020

### Summary on the product

Remdesivir 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, Nipah virus, and Hendra virus). Initial in vitro testing showed that remdesivir has potent antiviral activity against SARS-CoV-2 in Vero cells.

The pharmacokinetic (PK) profile of remdesivir in nonhuman primates and other relevant animal species supports once-daily intravenous (IV) administration as a 30-minute infusion.

Remdesivir is not authorised in any country. Remdesivir is currently used in clinical trials (P.R. China, US) or through compassionate use.

### Dosage and administration

To date, no dose is recommended by the company. The dose most frequently encountered is a loading dose of 200 mg IV over one hour followed by a maintenance of 100 mg IV over one hour during several days.

### Safety profile :

As of 14 February 2020, 4 Phase 1 clinical studies sponsored by Gilead have been conducted in which 138 healthy subjects have been dosed with remdesivir.

### A/ Clinical Trials sponsored by Gilead

#### Clinical trials

Trial	Study	N	Study population
GS-US-399-1812	Phase 1: single dose 3 to 225 mg	88	Healthy adults 18-55 Y
GS-US-399-1954	Phase 1: 150 mg for 7 or 14 days	16	Healthy adults 18-55 Y
GS-US-399-4231	Phase 1: radiolabelled remdesivir	6	Health males 18-45 Y
GS-US-399-5505	Phase 1: 200mg followed by 100 mg for 4 or 9 days	28	Healthy adults 18-45 Y

## Adverse events

Table 1: Adverse events occurring in ≥5 subjects (Safety analysis set)

Preferred Term	Remdesivir (N= 138)*
Phlebitis	8 (study 5505)
Constipation	7
Headache	6
Ecchymosis	5
Nausea	5
Pain in extremities	5

\* includes 131 subjects who received remdesivir and 7 subjects who received placebo (still blinded). Data from studies GS-US-399-431 and GS-US-399-5505 are preliminary.

## Laboratory abnormalities

Laboratory abnormalities were classified in grade 1 or grade 2 categories. No grade 4 abnormality was detected. Those abnormalities were:

- Transient elevation of ALT/AST starting from day 5 to 25.
- Mild and reversible prothrombin time (PT) prolongation without graded changes in INR
- Mild hyperglycaemia in 4 subjects

## Other findings

No patterns of clinically relevant changes in vital signs or shifts in 12-lead ECGs were observed during the studies in healthy subjects.

## Warning

No evidence of nephrotoxicity in healthy subjects.

However, a 150-mg dose of the solution and lyophilized formulations of remdesivir contains 9 and 4.5 g, respectively, of SBECD<sup>1</sup>, for which the maximum recommended daily dose (based on an EMA safety review) is approximately 250 mg/kg. Because SBECD is renally cleared, subjects with moderate or severe renal impairment may have SBECD exposures greater than those with mild renal impairment or normal renal function. Measurement of eGFR<sub>CG</sub> should be performed while subjects are receiving remdesivir, particularly subjects with known renal impairment at the start of therapy. For subjects with an eGFR<sub>CG</sub> decrease of ≥ 50%, permanent discontinuation of Remdesivir treatment should be considered. Subjects should then be followed as clinically indicated until eGFR<sub>CG</sub> returns to baseline or is otherwise explained, whichever occurs first.

<sup>1</sup> SBECD = sulfobutylether β-cyclodextrin sodium is an inactive ingredient of remdesivir.

### **Drug interaction**

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

### **Pregnancy and lactation**

Remdesivir has not been studied in pregnant and lactating women. Effective contraceptive methods should be used.

In non-clinical reproductive toxicity studies, Remdesivir demonstrated no adverse effect on embryofetal development when administered to pregnant animal and no adverse events on male fertility. Embryonic toxicity was seen when remdesivir was initiated in female animals prior to mating and conception, but only at a systematically toxic dose.

### **B/ Non-Gilead sponsored clinical studies**

Two studies were conducted in the Ebola context. PREVAIL IV was conducted in man who survived Ebola virus infection ( n=38) and PALM investigated treatment for patients with EVD (n=175 patients treated with remdesivir). PALM study included a small number of children (26%) and pregnant women (3%).

In both studies, the loading dose was 200 mg IV over an hour with a maintenance dose with 100 mg IV over one hour daily for 4 days in PREVAIL study and 9 to 13 days in PALM study.

No additional safety information was collected from those studies, except for one patient who died from hypotension and cardiac arrest at the time of the loading dose in PALM study. That death could not really be distinguished from underlying EVD.

### **C/ Additional experience with Remdesivir: Expanded access**

Six patients received remdesivir in the Ebola context and one US patient in the COVID-19 context. No new safety information was identified.