

Notes on the Design of Bioequivalence Study: Remdesivir

Notes on the design (or waiver) of bioequivalence studies for products invited for submission to the WHO Prequalification Unit – Medicines Assessment Team (PQT/MED) are issued to aid manufacturers with the development of their product dossier. Deviations from the approach suggested below can be considered acceptable if justified by sound scientific evidence.

The current notes should be read and followed in line with the general guidelines of submission of documentation for WHO prequalification. In particular, please consult the "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability". In: *Fifty-seventh Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization, 2024. WHO Technical Report Series, No. 1052, Annex 8.

Below, additional specific guidance is provided on the invited products containing remdesivir.

Pharmacokinetics of remdesivir¹

Following single-dose, 2-hour IV administration of remdesivir solution formulation at doses ranging from 3 to 225 mg, remdesivir exhibited a linear PK profile. Following single-dose, 2-hour IV administration of remdesivir at doses of 75 and 150 mg, both the lyophilized and solution formulations provided comparable PK parameters (AUC_{inf} , AUC_{last} , and C_{max}), indicating similar formulation performance. Remdesivir 75 mg lyophilized formulation administered IV over 30 minutes provided similar peripheral blood mononuclear cell (PBMC) exposure of the active triphosphate metabolite GS-443902 as remdesivir 150 mg lyophilized formulation administered IV over 2 hours. Following a single 150 mg intravenous dose of [^{14}C]-remdesivir, mean total recovery of the dose was >92%, consisting of approximately 74% and 18% recovered in urine and feces, respectively. The majority of remdesivir dose recovered in urine was metabolite GS-441524 (49%), while 10% was recovered as remdesivir.

Dosage forms, strengths and inactive ingredients of the comparator product¹

Lyophilized Powder

Remdesivir for injection, 100 mg, is a sterile, preservative-free lyophilized powder that is to be reconstituted with 19 mL of Sterile Water for Injection and further diluted into 0.9% sodium chloride infusion bag prior to administration by intravenous infusion.

Injection Solution

Remdesivir injection, 100 mg/20 mL (5 mg/mL), is a sterile, preservative-free, clear, colorless to yellow, aqueous-based concentrated solution that is to be diluted into 0.9% sodium chloride infusion bag prior to administration by intravenous infusion.

The inactive ingredients are sulfobutylether- β -cyclodextrin sodium salt (SBECD), water for Injection, and may include hydrochloric acid and/or sodium hydroxide for pH adjustment. Remdesivir for injection, 100 mg, contains 3 g SBECD, and remdesivir injection, 100 mg/20 mL (5 mg/mL), contains 6 g SBECD.

Guidance for the waiver of bioequivalence studies:

Considering the route of administration and inactive ingredients of the comparator product of remdesivir, the following guidance should be taken into account:

Multisource pharmaceutical products are considered to be equivalent without the need for further documentation when the pharmaceutical product is to be administered parenterally (e.g. intravenously, subcutaneously or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations to those in the comparator product. Certain excipients (e.g. buffer, preservative and antioxidant) may be different provided it can be shown that the change(s) in these excipients would not affect the safety and/or efficacy of the pharmaceutical product.

The EoI² includes:

- Remdesivir 100mg/20ml (5mg/ml) concentrate for solution for infusion
- Remdesivir 100mg powder for concentrate for solution for infusion (to be constituted to 20ml solution containing 5mg/ml of Remdesivir for further dilution for infusion)

Taking into account that SBECD is a critical excipient to keep the active pharmaceutical ingredient in solution, it is recommended to use the same qualitative and quantitative composition of inactive ingredients as the comparator product for a waiver of the in vivo bioequivalence study (i.e. 6 g of SBECD in Remdesivir 100mg/20ml (5mg/ml) concentrate for solution for infusion and 3 g of SBECD in Remdesivir 100mg powder for concentrate for solution for infusion). Any change in the type or amount of cyclodextrin or the use of alternative solubilizing strategies (e.g. micellar formulation) may require additional data to demonstrate equivalent performance and similar safety profile. Requirements will depend on composition of the proposed product.

References

1. Fact sheet for health care providers emergency use authorization (EUA) of remdesivir (GS-5734TM) at: <https://www.fda.gov/media/137566/download>. Accessed on 06/07/2020.
2. Invitation to Manufacturers of therapeutics against COVID-19 to submit an Expression of Interest (EOI) for Product Evaluation to the WHO Prequalification Team: Medicines