Notes on the Design of Bioequivalence Study: Ribavirin

Notes on the design of bioequivalence studies with products invited to be submitted to the WHO Prequalification Team – Medicines (PQTm) 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.


Below, additional specific guidance is provided on the invited immediate release products containing ribavirin.

Pharmacokinetics of ribavirin

There is a linear relationship between dose and AUC following single doses of 200-1,200 mg ribavirin. Ribavirin is absorbed rapidly following oral administration of a single dose with a mean Tmax = 1.5 hours. Single dose half-life is 80 hours. The bioavailability of a single oral dose of ribavirin was increased by co-administration of a high fat meal (AUC and Cmax both increased by 70 %). Ribavirin should be administered orally with food.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of ribavirin the following guidance with regard to the study design should be taken into account:

**Design:** A cross-over design is recommended.

**Dose:** As the EoI includes 200, 400 and 600 mg capsules, the highest strength of 600 mg should be employed in the bioequivalence study. However, if ribavirin is shown to be a highly soluble drug according to the BCS classification system, the bioequivalence study could be conducted with any strength. Further, if the Applicant generates the solubility data and stability data in the physiological pH range and classifies the drug according to the BCS criteria as highly soluble, ribavirin could be classified as BCS class III drug and a BCS biowaiver could be applicable.

For the 40 mg/ml syrup the dose of 600 mg should be administered but, if as it seems ribavirin could be classified as a BCS class III API, any therapeutic dose could be administered. The bioequivalence study could be waived if the test product contains the same excipients (i.e. glycerol, sucrose, sorbitol liquid (crystallising), propylene glycol) in similar concentrations as the comparator. Buffers, preservatives and flavours could be changed (i.e. sodium citrate, citric acid anhydrous, sodium benzoate, bubble gum flavouring).
**Fasting/fed:** As ribavirin should be taken with food, bioequivalence should be investigated in fed state.

**Subjects:** Healthy adult subjects should be utilized. It is not necessary to include patients in the bioequivalence study.

**Sample size:** Information currently available to PQTm indicates that the intra-subject variability for ribavirin is around 15 - 20%. These data may facilitate the calculation of a sufficient sample size for the bioequivalence study.

**Washout:** Taking into account the elimination half-life of ribavirin in the fed state of 80 hours, a washout period of 5 or 6 weeks is considered sufficient to prevent carry over.

**Blood sampling:** The blood sampling should be intensive for the first hours after administration to properly characterize the $C_{\text{max}}$ of ribavirin. For example, blood samples might be taken at pre-dose, 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 6, 8, 10, 12, 24, 48 and 72 h after drug administration. It is not necessary to take samples after 72 hours.

**Analytical considerations:** Information currently available indicates that it is possible to measure ribavirin in human plasma using LC-MS/MS analytical methodology. The bioanalytical method should be sufficiently sensitive to detect concentrations that are 5% of the $C_{\text{max}}$ in most profiles of each formulation (test or comparator).

**Parent or metabolite data for assessment of bioequivalence:** The parent drug is considered to best reflect the biopharmaceutical quality of the product. The disposition of ribavirin should be characterized, and the determination of bioequivalence will be based on the parent compound.

**Statistical considerations:** The data for ribavirin should meet the following bioequivalence standards in a single-dose, crossover design study:

- The 90% confidence interval of the relative mean $AUC_{0-72h}$ of the test to reference product should be within 80–125%

- The 90% confidence interval of the relative mean $C_{\text{max}}$ of the test to reference product should be within 80–125%.