Notes on the Design of Bioequivalence Study: Ledipasvir

Notes on the design of bioequivalence studies with products invited for submission to the WHO Prequalification Team – Medicines (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-first Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization, 2017. WHO Technical Report Series, No. 1003, Annex 6.

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

Pharmacokinetics of ledipasvir

Following oral administration of ledipasvir/sofosbuvir to hepatitis C-infected patients, ledipasvir median peak plasma concentration is observed at 4.0 hours post-dose. Ledipasvir AUC is dose-proportional over the dose range of 3 to 100 mg. Relative to fasting conditions, the administration of a single dose of ledipasvir/sofosbuvir with a moderate-fat or high-fat meal does not significantly affect the exposure to ledipasvir. The combination of sofosbuvir and ledipasvir can be administered without regard to food.

The median terminal half-life of ledipasvir in healthy volunteers following administration of ledipasvir/sofosbuvir in the fasted state is 47 hours.

Guidance for the design of bioequivalence studies

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

Design: A single-dose cross-over design is recommended.

Dose: As the EoI includes ledipasvir 90 mg tablet, the bioequivalence study should be conducted with this product vs. the fixed combination of sofosbuvir and ledipasvir as comparator product.

Fasted/fed: The bioequivalence study should be conducted in the fasted state as sofosbuvir/ledipasvir is recommended to be taken with or without food.

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

Parent or metabolite data for assessment of bioequivalence: The parent drug is considered to best reflect the biopharmaceutical quality of the product. The data for the parent compound should be used to assess bioequivalence of ledipasvir.

Sample size: Information currently available to PQT/MED indicates that the intra-subject variability in the fasted state for ledipasvir is approximately 45%. These data may facilitate the calculation of the sample size for the cross-over bioequivalence study.

Washout: Taking into account the elimination half-life of ledipasvir in healthy volunteers (approximately 47 hours), a washout period of 14 days is considered sufficient to prevent carry-over

Blood sampling: The blood sampling should be intense between 3 and 5 hours after drug administration to properly characterize the Cmax of ledipasvir. It is not necessary to take blood samples beyond 72 hours.

Analytical considerations: Information currently available to PQT/MED indicates that it is possible to measure ledipasvir 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_{max} in most profiles of each formulation (test or comparator).

Statistical considerations: The data for ledipasvir should meet the following bioequivalence standards in a single-dose, cross-over design study:

- The 90% confidence interval of the relative mean $AUC_{0\text{-}72\ h}$ of the test to comparator product should be within 80.00 – 125.00%.

- The 90% confidence interval of the relative mean C_{max} of the test to comparator product should be within 80.00 – 125.00%.

Information currently available to PQT/MED indicates that the comparator product is a highly variable drug product. Therefore, if the Applicant suspects that the variability of C_{max} or $AUC_{0\text{-}72h}$ is high (CV>30%), the applicant may prefer to employ a full replicate design study in order to widen the acceptance range of C_{max} and/or $AUC_{0\text{-}72\ h}$. For more information on replicate study designs and widening the limits of average bioequivalence, refer to Section 7.9.3 of Annex 6, TRS 1003 and PQT/MED guidance document “Application of reference-scaled criteria for AUC in bioequivalence studies conducted for submission to PQT/MED”.