Notes on the Design of Bioequivalence Study: Daclatasvir

Notes on the design of bioequivalence studies with 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 may be considered acceptable if justified by sound scientific evidence.

The current notes should be read and followed in line with the general guidelines for 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 daclatasvir.

Pharmacokinetics of daclatasvir

Daclatasvir administered as a tablet is readily absorbed following multiple oral doses with peak plasma concentrations occurring between 1 and 2 hours. Daclatasvir C_{max}, AUC, and C_{min} increased in a near dose-proportional manner.

In healthy subjects, administration of daclatasvir 60 mg tablet after a high-fat meal decreased daclatasvir C_{max} and AUC by 28% and 23%, respectively, compared with administration under fasting conditions. Administration of daclatasvir 60 mg tablet after a light meal resulted in no reduction in daclatasvir exposure.

Following multiple-dose administration of daclatasvir in hepatitis C-infected patients, the terminal elimination half-life of daclatasvir ranged from 12 to 15 hours.

Guidance for the design of bioequivalence studies

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

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

Dose: As daclatasvir is marketed as 30 mg, 60 mg and 90 mg tablets, but only the 30 mg and 60 mg strengths are included presently in the EoI, a 60 mg dose using the 60 mg tablet strength should be used in the bioequivalence study, since the pharmacokinetics are reported to increase with dose in a nearly dose-proportional manner.

Fasted/fed: The bioequivalence study should be conducted in the fasted state as daclatasvir may be taken with or without meals.

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 daclatasvir.

Sample size: Daclatasvir C_{max} in the fasted state has a low to moderate intra-subject variability (17–20%). These data may facilitate the calculation of a sufficient sample size for a cross-over bioequivalence study.

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

Blood sampling: The blood sampling for daclatasvir should be intensive in the first three hours after administration to properly characterize the C_{max} of daclatasvir. 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 daclatasvir 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 daclatasvir should meet the following bioequivalence standards in a single-dose crossover design study:

- The 90% confidence interval of the relative mean AUC_{0-t} of the test to reference product should be within 80.00–125.00%
- The 90% confidence interval of the relative mean C_{max} of the test to reference product should be within 80.00–125.00%.