Notes on the Design of Bioequivalence Study: Ivermectin

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 can be considered acceptable if justified by the applicant 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 ivermectin.

Pharmacokinetics of Ivermectin

Ivermectin is a mixture containing at least 90% 5-O-demethyl-22,23-dihydroavermectin A_{1a} and less than 10% 5-O-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)avermectin A_{1a}, generally referred to as 22,23-dihydroavermectin B_{1a} and B_{1b} , or H_2B_{1a} and H_2B_{1b}, respectively.

Following oral administration of ivermectin, plasma concentrations are approximately proportional to the dose. In two studies, after single 12 mg doses of ivermectin tablets in fasting healthy volunteers (representing a mean dose of 165 mcg/kg), the mean peak plasma concentrations of the major component (H_2B_{1a}) were 46.6 (±21.9) (range: 16.4-101.1) and 30.6 (±15.6) (range: 13.9-68.4) ng/mL, respectively, at approximately 4 hours after dosing.

Ivermectin is metabolized in the liver and ivermectin and its metabolites are excreted almost exclusively in the feces over 12 days, with less than 1% of the administered dose excreted in the urine. The elimination of ivermectin is multi-phasic with an initial half-life of approximately 18 hours and a longer terminal half-life of approximately 53 hours following oral administration.

Administration of 30 mg ivermectin following a high-fat meal resulted in an approximate 2.5-fold increase in bioavailability relative to administration of 30 mg ivermectin in the fasted state. Ivermectin tablets should be taken on an empty stomach with water.

Guidance for the Design of Bioequivalence Studies

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

Dose: As ivermectin is marketed presently as 3 mg tablets only, the use of a single tablet is recommended to reduce the variability that can be caused by different gastric emptying times of the different tablets, unless a higher therapeutic dose is necessary for bioanalytical reasons (i.e. insufficient lower limit of quantitation to detect levels of 5% of C_{max}). However, if additional strengths are developed in the future in order to simplify the administration by reducing the pill burden, the new higher strengths should be tested unless it is shown that ivermectin is a highly soluble drug.

Fasted/fed: The bioequivalence study should be conducted in the fasted state as ivermectin should be administered in fasted state.

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. Therefore, bioequivalence should be based on the determination of ivermectin B_{1a}.

Sample size: There is limited data on intra-subject variability of ivermectin $AUC_{0\text{-}72h}$ and C_{max} in humans in the fasted state. These limited data suggest that variability is >30% (29.3 – 44.3% for C_{max} and 24.9 – 34.0% for AUC). These data may facilitate the calculation of a sufficient sample size for the cross-over bioequivalence study.

Washout: Taking into account the elimination half-life of ivermectin in the fasted state of about 53 hours, a washout period of approximately 4 weeks is considered sufficient to prevent carry over.

Blood sampling: Blood sampling should be more intensive between 2 and 6 hours after administration to properly characterize the C_{max} of ivermectin. Considering the elimination half-life, it is sufficient to take blood samples up to 72 hours after administration for the characterization of ivermectin pharmacokinetics. For example, samples can be taken pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 3.75, 4.0, 4.25, 4.5, 4.75, 5.0, 5.5, 6.0, 8.0, 10.0, 12.0, 18.0, 24.0, 36.0, 48.0 and 72.0 hours after dosing.

Analytical considerations: Information currently available to PQT/MED indicates that it is possible to measure ivermectin B_{1a} in plasma using LC-MS/MS analytical methodology (with an LLOQ of 0.2 ng/ml). 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 ivermectin should meet the following bioequivalence standards in a single-dose crossover design study:

- The 90% confidence interval of the relative mean $AUC_{0\text{-}72h}$ 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%.

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 $AUC_{0\text{-}t}$. 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”.