Notes on the Design of Bioequivalence Study:
Ivermectin

Notes on the design of bioequivalence studies are issued to advise applicants on how to plan and conduct such studies with products invited for submission to the WHO Prequalification Team: medicines. Deviations from the approach suggested below can be considered acceptable if duly justified by the applicant by presenting sound scientific evidence.


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\textsubscript{1a} and less than 10% 5-O-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)avermectin A\textsubscript{1a}, generally referred to as 22,23-dihydroavermectin B\textsubscript{1a} and B\textsubscript{1b}, or H\textsubscript{2}B\textsubscript{1a} and H\textsubscript{2}B\textsubscript{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\textsubscript{2}B\textsubscript{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/or its metabolites are excreted almost exclusively in the feces over an estimated 12 days, with less than 1% of the administered dose excreted in the urine. The plasma half-life of ivermectin is approximately 18 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 bio-analytical reasons (i.e. insufficient lower limit of quantitation to detect levels of 5% of C\textsubscript{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.

**Fasting/fed:** The bioequivalence study should be conducted in the fasting state as ivermectin should be administered in fasting state.
**Subjects:** Healthy adult subjects should be used. It is not necessary to include patients in the bioequivalence study.

**Analytical considerations:** The measurement of ivermectin B$_{1a}$ in plasma is feasible (LLOQ = 0.2 ng/ml) and the use of the parent drug is considered to be more discriminative to differences in the biopharmaceutical performance of the drug products. 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$_{0-72h}$ and C$_{\text{max}}$ in humans in the fasting state. These limited data suggest that variability is >30% (approx. 30–40%). These data may facilitate the calculation of a sufficient sample size for the bioequivalence study, but they should be used cautiously since these data are obtained from an old study.

**Washout:** Taking into account the elimination half-life of ivermectin in the fasting state of about 18 hours, a washout period of approximately 1 week is considered sufficient to prevent carry over. However, this value should be employed cautiously since the existence of enterohepatic recycling may modify this value.

**Blood sampling:** Blood sampling should be more intensive between 2 and 6 hours after administration to properly characterize the C$_{\text{max}}$ 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.

**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$_{1a}$.

**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$_{0-72h}$ 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%.

Information currently available to the PQTm suggests that the comparator product might be a highly variable drug product for AUC and C$_{\text{max}}$ when administered in the fasting state. Therefore, if the Applicant suspects that the variability of C$_{\text{max}}$ is high (CV>30%), the Applicant may prefer to employ a replicate design study for at least the comparator product in order to scale the acceptance range of C$_{\text{max}}$. For more information on replicate study designs and average scaled bioequivalence, refer to Section 7.9.3 of Annex 7, TRS 992.

**Biowaiver:** Ivermectin does not appear to be a BCS Class I or III drug (high solubility drug) and the comparator product does not appear to demonstrate complete dissolution in less than 30 or 15 minutes in dissolution media at pH 1.2, 4.5 and 6.8 without surfactant, since the QC method of the comparator product contains 0.5% of SDS at pH 7.0. However, if the applicant was able to demonstrate the high solubility of ivermectin according to the BCS classification based on the highest therapeutic single dose, a BCS biowaiver would be feasible with the corresponding requirements for BCS Class I or III drugs (see Annex 7, TRS 992 for more information.)