Notes on the Design of Bioequivalence Study: Misoprostol

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 misoprostol.

Therapeutic indications and routes of administration of misoprostol

The current WHO treatment guidelines recommend misoprostol for a range of therapeutic indications, employing a variety of routes of administration as follows:

- In settings where oxytocin is unavailable:
  - Prevention of postpartum haemorrhage (PPH): oral misoprostol 600 µg.
  - Treatment of postpartum haemorrhage (PPH): sublingual misoprostol 800 µg.
- Spontaneous and Induced Abortion: oral, vaginal, buccal, or sublingual misoprostol (at different doses and regimens depending on factors such as gestational age at the time of administration); and
- For the induction of labour: vaginal misoprostol 25 µg.

To maximize a product's utility for treatment programmes and to avoid confusion in the clinical setting, prequalified misoprostol products should be suitable for use for all of the above noted indications. However, bioequivalence between the proposed and comparator products demonstrated following oral administration as discussed above cannot necessarily be extrapolated to the other routes of administration. In order to obtain the full range of indications for a prequalified product, the following data would be required in addition to the study employing oral administration:

- Data from a single-dose, cross-over bioequivalence study employing buccal administration. Proof of bioequivalence in this study would be considered sufficient information to grant indications employing sublingual, buccal, and vaginal routes of administration.
- Additional dissolution data will be needed in order to accept the product for the indication of "induction of labour" due to the required administration of fractional doses.

BCS-based biowaiver of misoprostol containing products

WHO considers misoprostol (in 1% HPMC dispersion) to be a BCS Class III API; therefore, a BCS-based biowaiver application is possible for multisource misoprostol products. Refer to the ICH Harmonised Guideline M9 *Biopharmaceutics Classification System-based Biowaivers* and the PQT/MED document *PQT/MED-specific Annotations for the ICH M9 Guideline* for more information on biowaiver applications.

It is noted that the qualitative and quantitative formulation of a recognized comparator product is available publicly. Therefore, it is possible for potential manufacturers of multisource misoprostol products to meet the excipient requirements for a product containing a BCS Class III API. That is, it is possible for manufacturers to produce a product that has a qualitatively the same and quantitatively very similar excipient composition in comparison to the comparator product. If the proposed product and comparator product are also very rapidly dissolving across the relevant pH range, then a BCS-based biowaiver can be granted.

Normally, a BCS-based biowaiver would only be applicable to products for the route of oral administration, however, in this case, if the test and comparator products meet qualitative and quantitative similarity requirements for excipients and both products demonstrate very rapid dissolution, WHO will waive the bioequivalence study requirements for all routes of administration.

Pharmacokinetics of misoprostol

When administered orally, misoprostol, an ester, is rapidly and completely de-esterified to pharmacologically active carboxylic acid in the stomach. Misoprostol acid is rapidly absorbed following oral administration, with peak plasma levels of the active metabolite misoprostol acid occurring after about 30 minutes. The plasma elimination half-life of misoprostol acid is 20 – 40 minutes. Concomitant ingestion of food decreases the bioavailability of oral misoprostol. Therefore, misoprostol should preferably be administered in the fasted state.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of misoprostol the following guidance with regard to the study design should be taken into account if the above mentioned BCS-based biowaiver is not applicable:

Design: A single-dose cross-over design for the oral route and another for the buccal route of administration are recommended.

Dose: As the EoI includes 200 microgram tablets and 25 microgram tablets, the bioequivalence study should be conducted with the high strength and the lowest strength could be waived if the conditions for an additional strength biowaiver were fulfilled.

Fasted/fed: As misoprostol should be taken preferably in fasted state, fasted state studies are recommended.

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

Parent or metabolite data for assessment of bioequivalence: Misoprostol is completely and rapidly de-esterified to misoprostol acid in the stomach. Therefore, bioequivalence for misoprostol should be based on the determination of the active metabolite misoprostol acid.

Sample size: Misoprostol acid C_{max} seems to be moderately variable (21 – 27%) after oral administration. These data may facilitate the calculation of a sufficient sample size for a cross-over bioequivalence study. However, no data is available for the buccal route of administration.

Washout: Taking into account the elimination half-life of misoprostol acid in healthy volunteers of 20 – 40 minutes, a washout period of a few days 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_{max} of misoprostol acid. It is not necessary to take blood samples beyond 10 hours for the characterization of the pharmacokinetics of misoprostol acid. For example, samples can be taken pre-dose and at 0.083, 0.167, 0.250, 0.333, 0.500, 0.667, 0.830, 1.000, 1.250, 1.500, 1.750, 2.000, 2.500, 3.000, 3.500, 4.000, 6.000, 8.000 and 10.000 hours.

Analytical considerations: Information currently available indicates that it is possible to measure misoprostol acid in human plasma using LC-MS/MS analytical methodology (e.g. 5 pg/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 misoprostol acid 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 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%.