Draft Guidance on Midostaurin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Midostaurin

Dosage Form; Route: Capsule; oral

Recommended studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in-vivo
   Strength: 25 mg
   Subjects: Healthy males and non-pregnant, non-lactating females.
   Additional Comments: Ensure that there are adequate washout periods between treatments in the crossover study due to the long terminal elimination half-life of one of the pharmacologically active metabolites CGP52421 of midostaurin. Also, consider using a parallel study design due to Midostaurin’s active metabolite CGP52421’s long half-life. For either a crossover or parallel study, sample collection time should be adequate to ensure completion of gastrointestinal transit of the drug product and absorption of the drug substance. Collect sufficient blood samples in the bioequivalence studies to adequately characterize the peak concentration (Cmax) and time to reach peak concentration (tmax).

2. Type of study: Fed
   Design: Single-dose, two-way crossover in-vivo
   Strength: 25 mg
   Subjects: Healthy males and non-pregnant, non-lactating females.
   Additional comments: Same as above.

Analytes to measure (in appropriate biological fluid): Midostaurin and its pharmacologically active metabolites CGP52421 (7-hydroxylation, epimer 2) and CGP62221 (O-demethylation) metabolites in plasma.

Submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.

Bioequivalence based on (90% CI): Midostaurin

Recommended Sept 2018
Waiver request of in-vivo testing:  N/A

Dissolution test method and sampling times:  The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location:  http://www.accessdata.fda.gov/scripts/cder/dissolution/.  Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products.