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Draft Guidance on Hydroxyurea

February 2023

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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.

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Active Ingredient: Hydroxyurea

Dosage Form; Route: Capsule; oral

Recommended Studies: Two options: (1) Biopharmaceutics Classification System (BCS) I-based biowaiver or (2) one in vivo bioequivalence study with pharmacokinetic endpoints

I. Option 1: BCS Class I-based biowaiver

A waiver request of in vivo testing for all the strengths of this product provided that the appropriate documentation regarding high solubility, high permeability and rapid dissolution as detailed in the most recent version of the FDA guidance for industry on *M9 Biopharmaceutics Classification System-Based Biowaivers*[a] is submitted in the application. Applicants may use the information contained in the approved labeling of the reference product. Peer reviewed articles may not contain the necessary details of the testing for the Agency to make a judgment regarding the quality of the studies. A decision regarding the acceptability of the waiver request can only be made upon assessment of the data submitted in the application.

II. Option 2: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 500 mg
   Subjects: Adult male and non-pregnant and non-lactating female patients with sickle cell anemia with recurrent painful crises who are on stable regimens of hydroxyurea
   Additional comments: Monitor blood counts at baseline and throughout the study. Female patients of reproductive potential and male patients with female partner of reproductive potential should use effective contraception during the study and for at least 6 months after the study. Submission of an investigational new drug application is

required prior to the conduct of a bioequivalence study for a cytotoxic drug product (See 21 C.F.R § 320.31).

Analyte to measure: Hydroxyurea in plasma

Bioequivalence based on (90% CI): Hydroxyurea

Waiver request of in vivo testing: 200 mg, 250 mg, 300 mg, and 400 mg strengths based on (i) acceptable bioequivalence study on the 500 mg strength, (ii) acceptable dissolution testing across all strengths, and (iii) proportional similarity in the formulations across all strengths

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, 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. Specifications will be determined upon review of the Abbreviated New Drug Application (ANDA).

Revision History: Recommended August 2008; Revised February 2023

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[a] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.