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Draft–Not for Implementation

Draft Guidance on Azacitidine

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Azacitidine

Dosage Form: Tablet

Route: Oral

Strengths: 200 mg, 300 mg

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: See additional comments
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 300 mg
   Subjects: Patients with acute myeloid leukemia who achieved first complete remission or complete remission with incomplete blood count recovery following intensive induction chemotherapy and are not able to complete intensive curative therapy
   Additional comments: A single dose in vivo bioequivalence study for azacitidine tablets in patients should be conducted under actual conditions of use in clinical practice, for example, with or without food depending upon patients' routine of taking this medication. Exclude patients with expected changes in concomitant medications that can potentially affect the pharmacokinetics of azacitidine. Implement antiemetic prophylaxis and safety monitoring, including complete blood count, during the treatment as recommended in the labeling. Applicants may consider using a reference-scaled average bioequivalence approach for azacitidine. If using this approach, provide evidence of high variability in the bioequivalence parameters of AUC and/or Cmax (i.e., within-subject variability ≥ 30%). For detailed information on this approach, refer to the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.[a]

Submission of an investigational new drug application is required prior to the conduct of a bioequivalence study for a cytotoxic drug of azacitidine pursuant to 21 C.F.R § 320.31.

Analyte to measure: Azacitidine in plasma

Bioequivalence based on (90% CI): Azacitidine

Waiver request of in vivo testing: 200 mg strength based on (i) acceptable bioequivalence study on the 300 mg strength, (ii) acceptable in vitro dissolution testing between two strengths, and (iii) proportional similarity of the formulations between two 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 for each of two strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

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Unique Agency Identifier: PSG_214120

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