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Draft Guidance on Cladribine

August 2024

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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:	Cladribine
Dosage Form:	Tablet
Route:	Oral
Strength:	10 mg
Recommended Studies:	Two options: (1) Biopharmaceutics Classification System (BCS) III-based biowaiver or (2) one in vivo bioequivalence study with pharmacokinetic endpoints

I. Option 1: BCS Class III-based biowaiver

A waiver request of in vivo testing for this product may be considered provided that the appropriate documentation regarding high solubility, very rapid dissolution,[a] and the test product formulation is qualitatively the same and quantitatively similar as detailed in the most recent version of the FDA guidance for industry on *M9 Biopharmaceutics Classification System-Based Biowaivers*[b] is submitted in the application. 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. Study design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 10 mg
   Subjects: Patients with relapsing forms of multiple sclerosis who plan to receive the first or second treatment course of cladribine

Additional comments:

a. Cladribine can be administered with or without food per the labeling. For the purpose of a bioequivalence study, patients should be instructed to take the drug under similar food conditions during both periods of the study.
b. Implement screening recommendations and safety monitoring, including complete blood count, during the treatment as recommended in the labeling.
c. Exclude patients with expected changes in concomitant medications that can potentially affect the pharmacokinetics of cladribine.
d. Exclude pregnant or lactating females.
e. For subjects of reproductive health:
    - Females should use effective contraception during the study and for at least 6 months after the final dose. Females using systemically acting hormonal contraceptive should add a barrier method during the study and for at least 4 weeks after the last dose.
    - Males with female partners of reproductive potential should use effective contraception during the study and for at least 6 months after the last dose.
f. Conduct the study on a specific day (e.g., the first day) of each cycle within one treatment course. The same dose (e.g., 10 mg or 20 mg) should be given on the same day in each cycle.
g. Submission of an Investigational New Drug Application is required prior to the conduct of a bioequivalence study for a cytotoxic drug product such as cladribine (See 21 C.F.R § 320.31).

Analyte to measure: Cladribine in plasma

Bioequivalence based on (90% CI): Cladribine

Waiver request of in vivo testing: Not applicable

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 all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

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[a] Refer to the most recent version of the FDA guidance for industry on *Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances*. Applicants may submit comparative dissolution data between test and RLD and proposed test product formulations to FDA via a controlled correspondence to obtain feedback on the applicability of a BCS-based biowaiver request.
[b] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.