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Draft Guidance on Budesonide

November 2022

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Capsule, delayed release; oral

Recommended Studies: Two in vivo bioequivalence studies with pharmacokinetic endpoints and one in vitro comparative dissolution study

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 4 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Female subjects of reproductive potential should use effective contraception during the study and for one week after the last dose. Specific recommendations are provided below. Applicants may consider using a reference-scaled average bioequivalence approach for budesonide. If using this approach, provide evidence of high variability in the pharmacokinetic parameters (i.e., within-subject variability ≥30%) for the reference product. 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]

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 4 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: See comments above.

Analyte to measure: Budesonide in plasma

Bioequivalence based on (90% CI): Budesonide

Additional comments regarding the bioequivalence study with pharmacokinetic endpoints:

1. For the fasting study, the following pharmacokinetic parameters will be evaluated for bioequivalence based on 90% CI: Log-transformed area under the concentration (AUC) time curve from hour 4 to the last measurable time point (AUC_{4-t}), AUC from hour 0 to the last measurable time point (AUC_{0-t}), AUC from hour 0 extrapolated to infinite time ($AUC_{0-\infty}$), and maximum concentration (C_{max}). As supportive evidence, submit AUC from 0 hours to 4 hours (AUC_{0-4}) of comparable therapeutic outcome. At least four measurements of concentration are recommended for AUC_{0-4} and at least four non-zero measurements of concentration are recommended for AUC_{4-t}.

2. For the fed study, the following pharmacokinetic parameters will be evaluated for bioequivalence based on 90% CI: Log-transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}. As supportive evidence, submit AUC_{0-4} and AUC_{4-t} data of comparable therapeutic outcome. At least four measurements of concentration are recommended for AUC_{0-4} and at least four non-zero measurements of concentration are recommended for AUC_{4-t}.

One in vitro comparative dissolution study:

1. Type of study: In vitro comparative dissolution study
   Strength: 4 mg
   Apparatus: United States Pharmacopoeia (USP) Apparatus 2 (paddle)
   Acid stage: 2 hours in 900 mL 0.1N HCl at 100 rpm
   Buffer stage: Each of
   pH 4.5 acetate buffer at 100 rpm
   pH 6.0 phosphate buffer at 100 rpm
   pH 7.2 phosphate buffer at 100 rpm
   Volume: 900 mL
   Temperature: 37ºC
   Sample times: As needed for profile comparison when applicable
   Additional comments: The applicant should use at least 12 dosage units for each of the test and reference products per test.

Additional strength: Not applicable

Dissolution test method and sampling times: For modified release drug products, applicants should develop specific discriminating dissolution methods. Alternatively, applicants may use the dissolution method set forth in any related official USP drug product monograph, or in the FDA's database, http://www.accessdata.fda.gov/scripts/cder/dissolution/, provided that applicants submit adequate dissolution data supporting the discriminating ability of such a method. If a new dissolution method is developed, submit the dissolution method development and validation report with the complete information/data supporting the proposed method. Conduct comparative dissolution testing on 12 dosage units for each of the test and reference products. Specifications will be determined upon review of the Abbreviated New Drug Application (ANDA).

Alcohol dose dumping studies: Due to concerns of dose dumping of drug from this product when taken with alcohol, conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium as follows:

Testing Conditions: 900 mL, 0.1N HCl, USP Apparatus 2 (paddle) at 100 rpm, with or without alcohol

> Test 1: 12 units tested according to the proposed method (with 0.1 N HCl) with data collected every 15 minutes for a total of 2 hours
>
> Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours
>
> Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours
>
> Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Conduct testing on both test and reference products accordingly, and provide data on individual unit, means, range and %CV.

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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.