

Draft Guidance on Budesonide

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Extended release capsule; oral

Recommended Studies: Four studies

1. Type of study: Fasting
Design: Single-dose, partially or fully replicated crossover design, in vivo
Strength: 3 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: Alternate study design is acceptable if appropriate. Specific recommendations are provided below. Female subjects of child-bearing potential should practice abstinence or contraception.
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2. Type of study: Fed
Design: Single-dose, partially or fully replicated crossover design, in vivo
Strength: 3 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: See comments in Study 1.
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3. Type of study: Fasting, sprinkle-in-applesauce
Design: Single-dose, partially or fully replicated crossover design, in vivo
Strength: 3 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: Mix the drug granules with the applesauce and keep the mixture for 30 minutes at room temperature before administration. See also comments in Study 1.
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Analyte to measure: Budesonide in plasma

Bioequivalence based on (90% confidence interval): Budesonide

Additional comments regarding the bioequivalence (BE) study with pharmacokinetic (PK) endpoints:

- (1). Applicants may consider using a reference-scaled average BE approach for budesonide. If using this approach, the applicant should provide evidence, from the

studies above, of high variability in the BE parameters (i.e., within-subject variability $\geq 30\%$) for the reference product. For general information on this approach, refer to the Progesterone Capsule Guidance for additional information regarding highly variable drugs.

(2). For Studies 1 and 3, the following PK parameters will be evaluated: Log-transformed AUC_{0-4} , AUC_{4-t} , $AUC_{0-\infty}$, and C_{max} , where AUC_{0-4} is the area under the plasma concentration vs. time curve from 0 to 4 hours, AUC_{4-t} is the AUC from 4 hours to the last measurable time point. Applicants should have extensive sampling points around T_{max} to have accurate estimation of C_{max} and T_{max} , and at least four non-zero measurements of concentration are recommended for each partial AUC. For the fed study, the following PK parameters will be evaluated: Log-transformed AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} . Applicants should submit AUC_{0-4} and AUC_{4-t} data as supportive evidence of comparable therapeutic outcome.

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4. Type of study: In vitro comparative dissolution study
Strength: 3 mg
Apparatus: U.S. Pharmacopoeia (USP) Apparatus 2 (paddle), with capsule sinker
Pretreatment stage: 2 hours in 1000 mL 0.1N HCl at 75rpm
Evaluation stage: Each of
- (1) pH 4.5 acetate buffer at 75rpm
 - (2) pH 6.0 phosphate buffer at 75rpm
 - (3) pH 6.5 phosphate buffer at 75rpm
 - (4) pH 6.8 phosphate buffer at 75rpm
 - (5) pH 7.2 phosphate buffer at 75rpm
 - (6) pH 7.5 phosphate buffer at 75rpm
- Volume: 1000 mL
Temperature: 37° C
Sample times: 0.5, 1, 1.5, 2, 2.5, 3, 4, 6 and 8 hours, or as needed for profile comparison
Additional comments: The applicant should use at least 12 dosage units of both the test and reference products per test.
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Additional strengths: Not applicable

Dissolution test method and sampling times (for product specification): For modified release drug products, FDA recommends that applicants develop specific discriminating dissolution methods. Applicants may also use the dissolution method set forth in any related official USP drug product monograph, or in the FDA's database (available at <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 for the modified release drug product, FDA recommends that the submission includes the dissolution method development and validation report with the complete information/data supporting the proposed method. 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.