Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Acetaminophen; Butalbital; Caffeine; Codeine Phosphate

October 2024

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Active Ingredients: Acetaminophen; Butalbital; Caffeine; Codeine phosphate

Dosage Form: Capsule

Route: Oral

Strength: 325 mg; 50 mg; 40 mg; 30 mg

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 325 mg; 50 mg; 40 mg; 30 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Females of reproductive potential should use effective contraception during the study. Acetaminophen; butalbital; caffeine; codeine phosphate capsule is under a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU). All pertinent elements of the REMS/ETASU are recommended to be incorporated into the protocol and informed consent.

Analytes to measure: Butalbital and codeine in plasma

Bioequivalence based on (90% CI): Butalbital and codeine

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 the test product and reference listed drug (RLD).[1] Specifications will be determined upon review of the abbreviated new drug application.

Document History: Recommended December 2014; Finalized August 2017; Revised October 2024

Unique Agency Identifier: PSG_020232

[1] If the RLD is not available, refer to the most recent version of the FDA guidance for industry on *Referencing Approved Drug Products in ANDA Submissions.*