Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Bismuth Subsalicylate; Metronidazole; Tetracycline Hydrochloride

February 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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 Ingredients: Bismuth subsalicylate; Metronidazole; Tetracycline hydrochloride

Dosage Form; Route: Tablet, chewable; oral

Bismuth subsalicylate chewable tablet is an over-the-counter (OTC) monograph drug and is generally recognized as safe and effective. Applicants may follow the corresponding OTC monograph (ID M008) for *Antidiarrheal Drug Products for Over-the-Counter Human Use*.[a]

Active Ingredients: Metronidazole; Tetracycline hydrochloride

Dosage Forms; Route: Tablet, capsule; oral

Recommended Studies: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strengths: 250 mg; 500 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comment: See specific comments below.

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strengths: 250 mg; 500 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comment: See specific comments below.

Analytes to measure: Metronidazole and tetracycline in plasma

Bioequivalence based on (90% CI): Metronidazole and tetracycline

Waiver request of in vivo testing: Not applicable

Additional comments regarding vivo bioequivalence studies with pharmacokinetic endpoints: For the above studies, applicants may either (1) reference previously submitted applications, e.g., Abbreviated New Drug Application (ANDA) or New Drug Application (NDA), for each individual drug product as the basis of submission for this co-packaged product; or (2) conduct two bioequivalence studies in total, one under fasting and one under fed conditions, by co-administering metronidazole tablet and tetracycline hydrochloride capsule; or (3) conduct four bioequivalence studies in total, both fasting and fed conditions for metronidazole tablet and tetracycline hydrochloride capsule separately. Applicants intending to submit separate ANDAs for metronidazole tablet and tetracycline hydrochloride capsule should follow the recommendations in individual product specific guidance and use the assigned reference standard of each drug product.

Dissolution test method and sampling times: The dissolution information for each component of this co-packaged 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 and reference products. Specifications will be determined upon evaluation of the ANDA.

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[a] For the most recent version of an OTC monograph, check the FDA monograph web page at https://www.accessdata.fda.gov/scripts/cder/omuf/.