Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Loperamide Hydrochloride; Simethicone

October 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form: Tablet, chewable

Route: Oral

Strength: 2 mg; 125 mg

Recommended Studies: One in vivo bioequivalence study with pharmacokinetic endpoints and one in vitro defoaming 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: 2 mg; 125 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: The tablet should be chewed, then swallowed with water.

One in vitro defoaming study:

1. Type of study: In vitro
   Conduct the U.S. Pharmacopeia (USP) in vitro defoaming study to measure the functional ability of simethicone to collapse bubbles produced by a foaming soap solution (1 g octoxynol-9/100 mL water). To demonstrate bioequivalence for the simethicone component, the following intro tests should be conducted: a) the USP in vitro defoaming testing, and b) the modified USP in vitro defoaming testing, wherein whole tablets are used instead of crushed tablets. The specification is a clear solution within 30 seconds.

Analyte to measure: Loperamide in plasma

Bioequivalence based on (90% CI): Loperamide

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 both strengths 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 August 2022; Revised October 2024

Unique Agency Identifier: PSG_020606

[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.*