

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Podofilox

August 2021

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This guidance, which interprets the Agency’s regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

In June 2012, FDA issued a draft product-specific guidance for industry on generic podofilox. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient: Podofilox

Dosage Form; Route: Gel; topical

Recommended Study: One study

1. Type of study: Bioequivalence (BE) Study with Clinical Endpoint
Design: Randomized, double blind, parallel, placebo-controlled in vivo
Strength: 0.5%
Subjects: Male or female with external anogenital warts
Additional comments: Specific recommendations are provided below.

Analytes to measure: Not Applicable

Bioequivalence based on (90% CI): Clinical endpoint

Waiver request of in vivo testing: Not Applicable

Dissolution test method and sampling times: Not Applicable

Additional comments regarding the BE study with a clinical endpoint:

1. The FDA recommends a BE study with a clinical endpoint comparing the podofilox topical gel, 0.5% test product versus the reference listed drug (RLD) and placebo control, with each subject applying the gel to the warts with the applicator tip or finger twice daily for 3 consecutive days, then discontinuing for 4 consecutive days. This one-week cycle of treatment is to be repeated until there is no visible wart tissue or for a maximum of four cycles (i.e., study product applied only on study Days 1, 2, 3, 8, 9, 10, 15, 16, 17, 22, 23, and 24). Application on the surrounding normal tissue should be minimized. Care should be taken to allow the gel to dry before allowing the return of opposing skin surfaces to their normal positions. Treatment should be limited to 10 cm² or less of wart tissue and to no more than 0.5 g of the gel per day.
2. The recommended primary endpoint of the study is the proportion of subjects in the per protocol (PP) population with “treatment success” defined as “total disappearance of all warts within all treated areas” at Week 4 (end of study). The “treatment success” is evaluated weekly and after four days (+5 days) of “rest” period after the last day of the last cycle of treatment. Five office visits are recommended: baseline (Day 0), Week 1 (Day 7), Week 2 (Day 14), Week 3 (Day 21) and Week 4 (Day 28). For determination of bioequivalence between products, statistical analysis of the primary endpoint should be conducted at Week 4 for all subjects.
3. Inclusion Criteria:
 - a. Healthy male or female aged ≥ 18 years with a clinical diagnosis of external anogenital warts (i.e., perianal warts and/or external genital warts), two or more distinct external genital warts, and wart area to be treated that is equal to or less than 10 cm². Histological confirmation should be obtained if there is any doubt of the diagnosis.
 - b. Females of childbearing potential may be enrolled if they were practicing a method of birth control with a reliability of at least 90%.
 - c. Any female subject with childbearing potential has a negative urine pregnancy test on first day of dosing (study Day 1).
 - d. Negative HIV test within 4 weeks before the first day of dosing (study Day 1).
4. Exclusion Criteria:
 - a. Pregnant or lactating or planning to become pregnant during the study period.
 - b. Known hypersensitivity or intolerance to podofilox or any component of the formulation.
 - c. History of previous unsuccessful treatment with any formulation of podofilox.
 - d. Mucous membrane wart, bowenoid papulosis, squamous cell carcinoma, or active herpes lesion within any treatment area.
 - e. Primary or secondary immunodeficiency.

- f. Local irritation in any treatment area that would interfere with treatment.
 - g. Use within 4 weeks prior to baseline of any: 1) treatment for anogenital warts, 2) systemic corticosteroid, or 3) systemic immunosuppressive drug.
5. The protocol should include a list of the prescription and over-the-counter drug products that are prohibited during the study, such as:
 - a. Any other topical products applied to the treatment area(s).
 - b. Systemic corticosteroid or immunosuppressive drugs.
 - c. Antipruritics, including antihistamines, within 24 hours of study visits.
 6. Instruct subjects to wash their hands thoroughly before and after each application of study product and to avoid contact with the eyes. If contact with the eyes occurs, subjects should immediately flush the eyes with copious quantities of water and seek medical advice. Inform subjects that the study product is flammable and to keep it away from open flames.
 7. Please provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
 - a. Study identifier
 - b. Subject identifier
 - c. Site identifier: study center
 - d. Age
 - e. Age units (years)
 - f. Sex
 - g. Race
 - h. Name of Actual Treatment (exposure): test product, RLD, placebo
 - i. First Dose of Assigned Treatment Date
 - j. First Dose of Assigned Treatment Time
 - k. Last Dose of Assigned Treatment Date
 - l. Last Dose of Assigned Treatment Time
 - m. Duration of Treatment (total number of days from first to last application, inclusive)
 - n. Per Protocol (PP) population inclusion (yes/no)
 - o. Reason for exclusion from PP population
 - p. Intent to Treat (ITT) population inclusion (yes/no)
 - q. Reason for exclusion from ITT population
 - r. Safety population inclusion (yes/no)
 - s. Reason for exclusion from safety population
 - t. Final designation as treatment success at Week 4 (yes/no)
 - u. Treatment compliance: number of missed doses per subject
 - v. Week 4 visit compliance (yes/no)
 - w. Concomitant medication (yes/no)
 - x. Adverse event(s) reported (yes/no)
 8. Please provide the basic data structure (BDS) dataset with records per subject, per visit, per analysis time point, using the following headers, if applicable:

- a. Study identifier
 - b. Subject identifier
 - c. Name of Actual Treatment (exposure): test product, RLD, placebo control
 - d. Visit number
 - e. Visit date
 - f. Number of days since baseline visit
 - g. Evaluator: identity of evaluator
 - h. Total number of anogenital warts within treatment area(s)
 - i. Total number of external genital warts
 - j. Total number of perianal warts
 - k. Skin reaction scores for each sign and symptom evaluated (e.g., erythema, dryness, burning/stinging, erosion, edema, pain, itching, bleeding, etc.)
 - l. Treatment success (yes/no)
 - m. Concomitant medication reported during this visit (yes/no)
 - n. Adverse event reported during this visit (yes/no)
 - o. Laboratory testing during this visit (yes/no)
 - p. Designation of treatment success at this visit (yes/no)
9. Please refer to the product-specific guidance on adapalene; benzoyl peroxide topical gel, 0.3%; 2.5% entitled *Guidance on Adapalene; Benzoyl Peroxide* for a recommended approach to statistical analysis and study design for bioequivalence studies with a clinical endpoint.
10. Study data should be submitted in a standardized format. Please refer to the study data standards published at www.fda.gov.¹

Revision History: Recommended June 2012; Revised August 2021

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¹ Study Data Standards Resources: <https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources>