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Draft Guidance on Asenapine

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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

This is a new draft product-specific guidance for industry on generic asenapine.

Active Ingredient: Asenapine

Dosage Form; Route: System; transdermal

Recommended Studies: One in vivo bioequivalence study with pharmacokinetic endpoints, one in vivo adhesion study, and one in vivo skin irritation and sensitization study

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
Design: Multiple-dose, steady-state, two-way crossover in vivo
Strength: 3.8 mg/24 hr
Subjects: Male and non-pregnant, non-lactating female patients who are receiving a stable daily dose of asenapine transdermal system, 3.8 mg/24 hr. FDA recommends that studies not be conducted using healthy subjects.
Additional comments:
 - In this document, this dosage form is referred to as a transdermal delivery system (TDS) and includes products that may be described elsewhere or known as *systems, patches or extended release films*.

- An equal number of patients should receive either the generic formulation or the reference formulation for the first period. The patients would then be switched to the other product for the second period. There should be no washout period between the two treatment periods.
- Unless otherwise justified, the asenapine TDS should be applied to the same anatomical site on all patients, selected from among those recommended for dosing in the approved labeling for the reference product, and worn for 24 hours. Applicants should randomize patients to receive either the test or reference product in a given study period. When possible, the TDS administered for each successive application should be applied to the same anatomical site, but on the contralateral side of the body.
- Refer to the current drug product labeling of the reference product, including BOXED WARNINGS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections and consider this information during study design and conduct, including attention to appropriate subject screening and selection, inclusion and exclusion criteria, and appropriate clinical safety monitoring. In addition:
 - Exclude subjects with severe hepatic impairment; a history of hypersensitivity reactions to asenapine or any components of the transdermal system; risk factors associated with prolonged QTc interval and Torsades de Points; or severe neutropenia (absolute neutrophil count <1000/mm³).
 - Monitor subjects with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur.
- Contact of the TDS with the skin is essential for the in vivo performance of the TDS, and the pharmacokinetics may be altered when a TDS loses its adherence to the skin. Therefore, the adhesion of each TDS should be monitored and recorded throughout the pharmacokinetic study. The applicant should prespecify their inclusion criteria for the statistical analysis of pharmacokinetic endpoints and perform their primary pharmacokinetic analysis on the per protocol population, however, pharmacokinetic samples should be collected and analyzed from all subjects at all sampling times regardless of the adhesion scores of the TDS and regardless of the inclusion criteria for the statistical analysis of pharmacokinetics. Provisions should be included in the study protocol to ensure that deliberate actions with the intent to re-apply a detached area of the TDS, to apply pressure to the TDS, or to reinforce TDS adhesion with the skin (e.g., overlays) are avoided throughout the study.
- The applicant should follow FDA's current thinking in the most recent version of the FDA guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*^a for the design and conduct of the pharmacokinetic bioequivalence study.

Analyte to measure: Asenapine in plasma

Bioequivalence based on (90% CI): Asenapine

In the evaluation of bioequivalence of the multiple dose study, the following pharmacokinetic data should be reported for asenapine:

- Individual and mean blood drug concentration levels in a dosing interval after steady state is reached
- Individual and mean trough levels ($C_{\min SS}$)
- Individual and mean peak levels ($C_{\max SS}$)
- Calculation of individual and mean steady-state $AUC_{0-\tau}$ ($AUC_{0-\tau}$ is AUC during a dosing interval at steady-state)
- Individual and mean percent fluctuation [$=100 * (C_{\max SS} - C_{\min SS})/C_{avSS}$]
- Individual and mean time to peak concentration ($T_{\max SS}$)

The 90% confidence interval for the ratio of the geometric means of the pharmacokinetic parameters ($AUC_{0-\tau}$ and $C_{\max SS}$) should be within 80-125%. Fluctuation for the test product should be evaluated for comparability with the fluctuation of the reference product. The trough concentration data should be analyzed (e.g., at least three consecutive measurements) to verify that steady state was achieved prior to period 1 and period 2 pharmacokinetic sampling. Pharmacokinetic data should be submitted to demonstrate that steady state has been reached for each individual.

Waiver request of in vivo testing: The 5.7 mg/24 hr and 7.6 mg/24 hr strengths of the TDS may be considered for a waiver of in vivo bioequivalence testing based on (i) an acceptable bioequivalence study with the 3.8 mg/24 hr strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the TDS formulation across all strengths

NOTE: The proportional similarity of the TDS formulation across all strengths means i) that the amounts of active and inactive ingredients per unit of active surface area are identical for the different strengths of the test product, and ii) that the ratios of the active surface areas of each strength of the test product compared to the 3.8 mg/24 hr strength of the test product are the same as the corresponding ratios for the active surface areas of each strength of the reference product compared to the 3.8 mg/24 hr strength of the reference product.

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 each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

2. Type of study: Adhesion study

Design: Single-dose, two-treatment, two-period crossover in vivo

Strength: 3.8 mg/24 hr

Subjects: Male and non-pregnant, non-lactating female patients who are receiving a stable daily dose of asenapine transdermal system 3.8 mg/24 hr

Additional comments:

- See additional comments above under Study 1 for the conduct of the adhesion study.

- The applicant may elect to evaluate the pharmacokinetic bioequivalence (study 1) and the adhesion (study 2) in a single study with a combined purpose, or in independent studies. In either case, the studies should be adequately powered to evaluate the bioequivalence, and independently, the comparative assessment of adhesion.
- The applicant should follow FDA's current thinking in the most recent version of the FDA guidance for industry *Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs*^a for the design and conduct of the independent adhesion study or the combined study to evaluate both pharmacokinetic bioequivalence and adhesion.

3. Type of study: Skin irritation and sensitization study

Design: Randomized, evaluator-blinded, within-subject, repeat design in vivo

Strength: Vehicle TDS and positive control equivalent to the size of 3.8 mg/24 hr or higher strength (TDS containing active pharmaceutical ingredient should not be used in this study due to safety concerns)

Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments:

- All test articles (i.e., vehicle TDS¹, positive control of low irritancy², and optional negative control³) should be applied simultaneously to each subject at different positions on an application site recommended in the in the approved labeling for the reference product.
- Sequential TDS applications should be made to the same application site every 24 hours for a total of 21 consecutive days.
- The applicant should follow FDA's current thinking in the most recent version of the FDA guidance for industry *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs*^a for the design and conduct of the skin irritation and sensitization study.

Additional information:

Device:

The reference listed drug (RLD) product is a transdermal delivery system and a drug-device combination product.

FDA recommends that prospective applicants examine the external critical design attributes of the RLD device when designing the test device.

¹ The optional vehicle TDS should contain all of the inactive ingredients in the test product and be identical to the test product in every manner except for the absence of the active ingredient.

² Safety concerns preclude the use of comparative studies with the test and reference products, therefore, the test product can be evaluated by testing a vehicle TDS versus a positive control TDS that produces mild irritation (e.g., ≤ 0.1% sodium lauryl sulfate).

³ An example of the optional negative control treatment is an occlusive cover or device with normal saline applied on a polyester pad under the cover or within the device chamber.

User Interface Assessment:

An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.^a

Unique Agency Identifier: PSG_212268

^a For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.