

Draft Guidance on Rotigotine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Active Ingredient: Rotigotine

Dosage Form; Route: Film, extended release; transdermal

Recommended Studies: Three studies

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 2 mg/24 hr
Subjects: Males and non-pregnant, non-lactating females, general population
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 *patches* or *extended release films*.
 - Unless otherwise justified, the rotigotine TDS should be applied to the same anatomical site on all subjects, selected from among those recommended for dosing in the approved labeling for the reference product, and worn for 24 hours. Applicants should randomize subjects to receive either the test or reference product in a given study period. When possible, the TDS administered in the second study period should be applied to the same anatomical site as in the first study period, but on the contralateral side of the body.
 - 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 pharmacokinetic endpoints. 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 guidance *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* for the design and conduct of the pharmacokinetic bioequivalence study.

Analytes to measure (in appropriate biological fluid): Rotigotine in plasma

Bioequivalence based on (90% CI): Rotigotine

Waiver request of in vivo testing: The 1 mg/24 hr, 3 mg/24 hr, 4 mg/24 hr, 6 mg/24 hr and 8 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 2 mg/24 hr strength TDS, (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 2 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 2 mg/24 hr strength of the reference product.

Dissolution test method and sampling times: Comparative dissolution testing should be conducted on 12 dosage units each, of all strengths of the test and reference products. Information on a dissolution method for this drug product can be found on the FDA Dissolution Methods web site, accessible at: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>.

2. Type of study: Adhesion study
 Design: Single-dose, two-treatment, two period crossover in vivo
 Strength: 2 mg/24 hr
 Subjects: Males and non-pregnant, non-lactating females, general population
 Additional comments:
- 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 guidance *Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs* 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 in vivo

Strength: 1 mg/24 hr or 2 mg/24 hr (Dose: 0.5 mg/24 hr, administered as either one-half of a 1 mg/24 hr TDS or one-quarter of a 2 mg/24 hr TDS)

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

Additional comments:

- All test articles (i.e., one-half of the 1 mg/24 hr test product,¹ one-half of the 1 mg/24 hr reference product, optional vehicle TDS² and optional negative control³ OR one-quarter of the 2 mg/24 hr test product¹, one-quarter of the 2 mg/24 hr reference product, optional vehicle TDS² and optional negative control³) should be applied simultaneously to each subject at different positions on an application site recommended for dosing 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 TDS applied on Day 21 should be removed on Day 22.
- There is insufficient information to determine whether it is safe to simultaneously apply two whole, active, 1 mg/24 hr or 2 mg/24 hr rotigotine TDS on the same subject during a 21-day skin irritation and sensitization study. Since the reference product has a matrix design that can be safely cut in half, one-half of the 1 mg/24 hr reference product or one-quarter of the 2 mg/24 hr reference product can be used for these studies. If the test TDS also has a design that can be safely cut to a smaller size, it should also be cut in half, and one half of the test product may be applied simultaneously with one half of a reference product (to separate skin sites). It would not be acceptable to manufacture a separate batch of the test product in order to use a smaller TDS in this study. If the test product has a design that cannot be safely cut to a smaller size, and/or if a prospective applicant proposes study design different than what is recommended above, the prospective applicant may submit a pre-abbreviated new drug application (pre-ANDA) meeting request to discuss the proposed approach.
- The sponsor should follow FDA's current thinking in the guidance *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs* for the design and conduct of the skin irritation and sensitization study.

Additional comments relating to all studies:

In addition to the recommendations in the general guidances referenced above, and the product specific recommendations related to the individual studies, the following product specific recommendations should be considered.

- Exclusion Criteria (the applicant may add additional criteria):

¹ The test product evaluated should be the actual TDS to be marketed.

² 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.

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

- a. History of sulfite sensitivity
 - b. Medical history of asthma, orthostatic hypotension, dizziness, syncope, or dyskinesia
 - c. History of hyper or hypotension
 - d. Clinically relevant findings in a screening 12-lead electrocardiogram, such as a second- or third-degree atrioventricular block, complete bundle branch block, or arrhythmias
 - e. History of narrow angle glaucoma
 - f. Taking monoamine oxidase inhibitors (MAOIs), reserpine, methyl dopa, antipsychotics, neuroleptics, clozapine, olanzapine, quetiapine, metoclopramide, or risperidone within 3 months of enrollment
 - g. Medical history of somnolence and/or having fallen asleep without warning
 - h. Medical history of psychotic disorder
- Provide a listing of the prescription and over-the-counter drug products that are contraindicated during the study, such as:
 - a. Central nervous system depressants (e.g., benzodiazepines, antipsychotics, antidepressants, MAOIs)
 - The backing layer of the reference contains aluminum. Subjects should be advised to remove all TDS products prior to magnetic resonance imaging or cardioversion to avoid skin burns.
 - Subjects should be alerted to the potential sedating effects associated with rotigotine, including somnolence and particularly to the possibility of falling asleep while engaged in activities of daily living. Since somnolence is a frequent adverse event with potentially serious consequences, patients should neither drive a car nor engage in other potentially dangerous activities until they have gained sufficient experience with their test product and reference product to gauge whether or not it affects their mental and/or motor performance adversely. Subjects should be advised that if increased somnolence or new episodes of falling asleep during activities of daily living (e.g., watching television, passenger in a car, etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities until they have contacted their physician.
 - Because of the possible additive effects, subjects should be advised to avoid alcohol while enrolled in the induction and challenge phases of the skin irritation and sensitization study.
 - Subjects should be advised to inform their physician if they experience new or increased gambling urges, increased sexual urges or other intense urges.