

Draft Guidance on Granisetron

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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: 3.1 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 granisetron TDS should be applied to the same anatomical site on all subjects, as recommended for dosing in the approved labeling for the reference product, and worn for 7 days. 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 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 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): Granisetron in plasma

Bioequivalence based on (90% CI): Granisetron

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Comparative dissolution testing should be conducted on 12 dosage units each, 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: 3.1 mg/ 24hr
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.
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3. Type of study: Skin irritation and sensitization study
Design: Randomized, evaluator-blinded, within-subject repeat in vivo
Strength: 3.1 mg/24 hr (Dose: One-half of 3.1 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 3.1 mg/24 hr test product¹, one-half of the 3.1 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 in the in the approved labeling for the reference product.

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 occlusive cover or device with normal saline applied on a polyester pad under the cover or within the device chamber.

- Sequential TDS applications should be made to the same application site every 7 days for a total of 21 consecutive days.
- There is insufficient information to determine whether it is safe to simultaneously apply two whole, active, 3.1 mg/24 hr granisetron 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 reference product can be used for these studies. If the test product 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 TDS has a design that cannot be safely cut to a smaller size, and/or if a prospective applicant proposes a 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 applicant 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.

- As a safety precaution, the subject's seated blood pressure should be evaluated at all visits.
- Inclusion Criteria (the applicant may add additional criteria):
 - a. Premenopausal females who have a negative pregnancy test at screening AND have undergone surgical sterilization OR agree to practice abstinence or contraception during the study.
 - b. Baseline systolic blood pressure should be no greater than 140 mm Hg and diastolic blood pressure no greater than 80 mm Hg.
- Exclusion Criteria (the applicant may add additional criteria):
 - a. History of sensitivity to granisetron or other components of the TDS
- A listing of the prescription and over-the-counter drug products that are contraindicated during the study should be provided, such as:
 - a. 5-HT₃ receptor antagonists other than test and reference products, e.g., alosetron hydrochloride, oral granisetron, dolasetron mesylate, ondansetron, palonosetron hydrochloride
 - b. Estrogens, other than study medication

- Subjects should be advised to cover the TDS application sites, e.g., with clothing, if there is a risk of exposure to sunlight throughout the period of wear and for 10 days following its removal because of a potential skin reaction.