Contains Nonbinding Recommendations

Draft Guidance on Clonidine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Film, extended release; transdermal

Recommended Studies: Three studies

1. Type of study: Bioequivalence (BE) study with pharmacokinetic (PK) endpoints
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 0.3 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 clonidine 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 listed drug (RLD) product, and worn for 7 days. Applicants should randomize subjects to receive either the test or RLD 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 PK 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 PK study. The PK samples should be collected and analyzed from all subjects at all sampling times regardless of the adhesion scores of the TDS. 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 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 PK BE study.

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

   Bioequivalence based on (90% CI): Clonidine

Waiver request of in vivo testing: The 0.1 mg/24 hr and 0.2 mg/24 hr strengths of the TDS may be considered for a waiver of in vivo BE testing based on (1) an acceptable BE study with the 0.3 mg/24 hr strength TDS, (2) acceptable in vitro dissolution testing of all strengths, and (3) proportional similarity of the TDS formulations 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 0.3 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 RLD product compared to the 0.3 mg/24 hr strength of the RLD 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 RLD 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/.

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2. Type of study: Adhesion study
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 0.3 mg/24 hr
Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments:

- The RLD TDS is supplied with an overlay (adhesive cover) that may be used when needed to reinforce the adhesion of the TDS to the skin. A drug product submitted in an ANDA should also be supplied with an adhesive overlay (either integrated into the TDS or co-packaged with the TDS).
- In addition to comparing the adhesive performance of the test and RLD product, the adhesive performance of the test and RLD co-packaged overlays should also be compared.
- If a prospective applicant proposes to develop a test TDS product that does not contain an overlay (either integrated into the TDS or co-packaged with the TDS), the prospective applicant may submit a pre-ANDA meeting request to discuss the proposed approach.
- The applicant may elect to evaluate the PK BE (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 BE, 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 PK BE 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: 0.1 mg/24 hr
Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments:

- All test articles (i.e., 0.1 mg/24 hr test product[1], 0.1 mg/24 hr RLD product, optional vehicle TDS[2] and optional negative control[3]) should be applied simultaneously to each subject at different positions on an application site recommended for dosing in the approved labeling for the RLD product.
- Sequential TDS applications should be made to the same application site every 7 days for a total of 21 consecutive days. The TDS applied on Day 15 should be removed on Day 22.
- In addition to comparing the irritation potential of the test and RLD products, the irritation potential of the test and reference co-packaged overlays should also be compared.
- 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.

- Subjects who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of a possible sedative effect of clonidine. They should also be informed that this sedative effect may be increased by concomitant use of alcohol, barbiturates, or other sedating drugs.

[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 is an occlusion cover or device with normal saline applied on a polyester pad under the cover or within the device chamber.

- Skin burns have been reported at the application site in several patients wearing an aluminized TDS during a magnetic resonance imaging (MRI) scan. Because the RLD contains aluminum, subjects should be advised to remove the test articles before undergoing an MRI.
- Adequate precautions should be taken to ensure patient safety during the study. These should include the following:
    a. Considering that this is an antihypertensive drug, it should be anticipated that it will result in a decrease in blood pressure, and criteria for exclusion and discontinuation of subjects considered potentially hypertensive or hypotensive should be included in the protocol. The protocol should contain stopping criteria for subjects who may become hypotensive during the course of the study.
    b. Consider confining patients during the first several days of the study to facilitate frequent monitoring of vital signs.
    c. Monitor vital signs at least daily throughout the first 7 days of the study and at the time of TDS changes thereafter.
    d. Subjects should return for three days after final TDS removal for monitoring of blood pressure and adverse event assessment to evaluate for the possibility of a rebound effect that can result in increased blood pressure following sudden withdrawal of clonidine therapy.
- Because addition of the active drug to a placebo TDS may potentially result in different irritation or adhesion characteristics, these studies should be conducted with the actual TDS to be marketed and the actual RLD product. The OGD has considered the safety of administering clonidine TDS to healthy volunteers continuously for 21 days and has determined that this study can be safely conducted using the lowest strength TDS (0.1 mg/day) and applying one test product TDS and one RLD TDS to each subject at the same time. Use of an additional vehicle TDS (e.g., having all of the inactive ingredients and being identical to the proposed product in every manner except for the absence of clonidine) is optional. Use of a negative control (e.g., normal saline) is also optional.
- Inclusion Criteria (the applicant may add additional criteria):
    a. Premenopausal female subjects have undergone surgical sterilization OR agree to practice abstinence or contraception during the study.
- Exclusion Criteria (the applicant may add additional criteria):
    a. Previous exposure to oral or transdermal clonidine or any adverse event or allergic reactions to other alpha 2-adrenergic agonists.
    b. Unwilling or unable to refrain from the use of alcohol during the study.
- Prohibiting use of the following medications during the study is recommended for safety reasons:

a. Monoamine oxidase inhibitors (MAOI), [e.g. Eldepryl (selegiline). tranylcypromine, phenelzine or isocarboxazid]

b. Tricyclic antidepressant medications (e.g. Elavil, Etrafon, Pamelor, Sinequan, Tofranil, Triavil) for depression

c. Antihypertensive medication (including all alpha agonists, β -blockers and calcium channel blockers, regardless of indication)

d. Drugs that affect the heart rate such as guanethidine, β-adrenergic blocking agents, (e.g. propranolol) cardiac glycosides, or sympathomimetic amines

e. Sedative hypnotic medication