Contains Nonbinding Recommendations

Draft Guidance on Selegiline

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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: 6 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 selegiline 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 24 hours. 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, 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 PK BE study.

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

   Bioequivalence based on (90% CI): Selegiline

Waiver request of in vivo testing: The 9 mg/24 hr and 12 mg/24 hr strengths of the TDS may be considered for a waiver of in vivo BE testing based on (i) an acceptable BE study with the 6 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 6 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 6 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: 6 mg/24 hr
Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments:

- 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: 6 mg/24 hr
Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments:

- All test articles (i.e., 6 mg/24 hr test product[1], 6 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 of the RLD 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.
- 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):
  a. Psychiatric illness requiring treatment.
  b. History of pheochromocytoma.
  c. Taking selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine, sertraline, and paroxetine); serotonin and norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine and duloxetine); the tricyclic antidepressants clomipramine and imipramine, the opiate analgesics meperidine, tramadol, methadone, pentazocine, and propoxyphene; and the antitussive agent dextromethorphan.
  d. Taking buspirone, amphetamines, or cold products or weight-reducing preparations that contain sympathomimetic amines (e.g., pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine).
- Provide a listing of the prescription and over-the-counter drug products that are contraindicated during the study, such as:
  a. Amphetamines
  b. Buspirone (anti-anxiety agent)
  c. Carbamazepine (antiepileptic)

[1] The test TDS evaluated should be the actual product 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 inactive 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.

d. Bupropion hydrochloride

e. Cyclobenzaprine (relieves muscle spasm)

f. Decongestants

g. Dextromethorphan (cough suppressant)

h. Dual serotonin and norepinephrine inhibitors (e.g., desvenlafaxine, duloxetine, venlafaxine)

i. Monoamine oxidase inhibitors other than test product and RLD (e.g., isocarboxazid, oral selegiline, rasagiline, phenelzine, tranylcypromine)

j. Methylphenidates (e.g., dexmethylphenidate, methylphenidate)

k. Narcotics and certain analgesics (e.g., cocaine, meperidine, methadone, pentazocine, propoxyphene, tramadol)

l. Oxcarbazepine (antiepileptic)

m. Sympathominetic amines [albuterol and metaproterenol (bronchodilators), midodrine (orthostatic hypotension)]

n. Tetracyclic antidepressants (e.g., mirtazapine)

o. St. John's wort

p. Tyramine containing over-the-counter supplements

- Provide a listing of foods and beverages that may cause adverse interactions with selegiline and should be avoided during the study, such as:

  a. Foods that have a high tyramine content, such as aged cheeses, fava or broad beam pods, sauerkraut, soy bean products, soy sauce, tofu, yeast extract, pickled herring, air dried, aged and fermented meats, sausages and salamis (e.g., cacciatore, hard salami, mortadella and pepperoni).

  b. All varieties of tap beer and beers that have not been pasteurized so as to allow for ongoing fermentation.

- Subjects should be advised that the use of alcohol is not recommended while taking study drug.

- Blood pressure should be assessed at each visit.