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VIA FEDERAL EXPRESS

Division of Docket Management
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fisher Lane, Room 1061
Rockville, MD 20852

Citizen Petition

Dear Sir or Madam:

The undersigned submits this Citizen Petition ("Petition") under Section 505 of the Federal Food, Drug and Cosmetic Act ("the Act") (21 U.S.C. 355 (2006)), and in accordance with 21 CFR 10.20, 10.30, 314. 94, 320.1 and 320.23-24.

The Petitioner respectfully requests that the Commissioner of the Food and Drug Administration (FDA) reconsider the bioequivalence requirements for nilutamide tablets as presented in FDA's *Guidance on Nilutamide* (October 2011; Attachment 1). Specifically, the Guidance requires that a steady-state, two-way crossover (or parallel) *in vivo* study is conducted in patients who are currently receiving the drug at a dose of 150 mg once a day. Presumably, this study design is recommended to assure that normal healthy volunteers are not subjected to deleterious effects of the antiandrogenic activity of the drug, or the potential safety risks such as hepatic injury or interstitial pneumonitis noted in the product label (Attachment 2). The Petitioner has reviewed these risks and believes that these risks can be mitigated through protocol design and proposes that FDA revise the Guidance to include the following design as an alternate to the current design:

- 2 Studies (fed and fasting)
- Single-dose, two-way crossover *in vivo*
- Normal healthy males (general population)
- Exclude female subjects
- Exclude subjects with severe hepatic impairment
- Exclude subjects with severe respiratory insufficiency
- Exclude subjects with hypersensitivity to nilutamide or any components of the drug products (i.e., test and reference products)
- An AUC truncated to 72 hours may be used in place of AUC_{0-t} or $AUC_{0-\infty}$

FDA-2013-P-0335

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Nilutamide is an antiandrogenic pharmaceutical therapy that complements surgical castration, which only suppresses testicular androgens. The combination of nilutamide with surgical castration is used in the treatment of metastatic prostate cancer. Prostate cancer is known to be androgen sensitive and responds to androgen ablation.

The androgenic response of a single 150 mg dose is expected to be minimal and reversible; therefore, the risk of a sustained deleterious effect is very low. According to the product label, both interstitial pneumonitis and hepatoxicity adverse events were rare and only observed in patients receiving chronic therapy. Therefore, the potential for these adverse events to occur in normal healthy subjects receiving two single 150 mg doses are very low and the risk can be further mitigated by excluding subjects that have severe hepatic impairment and/or severe respiratory insufficiency.

These safeguards are similar to those used for flutamide and bicalutamide, which have similar antiandrogenic pharmacology and analogous safety profiles (see labels presented in Attachment 3 and Attachment 4). It is further noted that the FDA *Guidance for Bicalutamide* (May 2008; Attachment 5) recommends studies that are similar to the proposed study design. Bioequivalence studies for these generic products were conducted in clinical studies that are similar to the proposed studies using normal healthy volunteers. Nilutamide does not appear to present an effect or safety profile that warrants and additional safeguards other than those already established for this class of drugs and are well understood of investigational review boards (IRBs).

A. Action Requested

This Petition requests that FDA amend the 2011 *Guidance for Nilutamide* to include the following design as an alternate to the current design:

- 2 Studies (fed and fasting)
- Single-dose, two-way crossover *in vivo*
- Normal healthy males (general population)
- Exclude female subjects
- Exclude subjects with severe hepatic impairment
- Exclude subjects with severe respiratory insufficiency
- Exclude subjects with hypersensitivity to nilutamide or any components of the drug products (i.e., test and reference products)
- An AUC truncated to 72 hours may be used in place of AUC_{0-t} or $AUC_{0-\infty}$

B. Statement of Grounds

The alternative study design does not present the potential for significant short-term or long-term deleterious antiandrogenic effects. The potential safety risks of hepatic injury or interstitial pneumonitis are rare and occur in patients receiving chronic therapy, and are otherwise mitigated by exclusion of subjects that are contraindicated for the drug.

C. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR 25.31. To the petitioner's knowledge, no extraordinary circumstances exist.

D. Economic Impact Statement

In accordance with 21 CFR 10.30(b), the petitioner will, upon the request by the Commissioner, submit economic impact information.

E. Certification

The undersigned certifies that, to his best knowledge and belief, this Petition includes all information and view on which the Petition relies, and it includes representative data and information known to the Petitioner, which are unfavorable to the Petition.

Sincerely yours,

David L. Rosen, BS Pharm., JD

Attachments:

Attachment 1: *Guidance on Nilutamide*, October 2011

Attachment 2: Nilandron® (nilutamide) Tablets Package Insert

Attachment 3: Eulexin® (flutamide) Capsules Package Insert

Attachment 4: Casodex® (bicalutamide) Tablets Package Insert

Attachment 5: *Guidance on Bicalutamide*, May 2008

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