4611 11 JUN 17 P1:57

novo nordisk®

June 17, 2011

BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, Maryland 20852

Re: Citizen Petition Regarding the Approval of Abbreviated New Drug Applications for Vagifem® (estradiol vaginal tablets) 10 and 25 mcg

Dear Sir or Madam:

CITIZEN PETITION

Novo Nordisk Inc. ("Novo Nordisk") submits this Citizen Petition pursuant to the Federal Food, Drug, and Cosmetic Act ("FDC Act") and the Food and Drug Administration's ("FDA's" or "the Agency's") implementing regulations at 21 C.F.R. § 10.30 to request that the Agency refrain from approving any Abbreviated New Drug Applications ("ANDAs") for 10 or 25 mcg generic versions of Vagifem® (estradiol vaginal tablets) unless the applicant conducts well-controlled multiple endpoint clinical bioequivalence studies. Because Novo Nordisk no longer

Novo Nordisk Inc.
Jeremy Berger
Senior Litigation Attorney
100 College Road, West
Princeton, New Jersey 08540
USA
Telephone:
609-786-4883
Fax:
609-987-5440
E-mail:
jybg@novonordisk.com
Internet:
www.novonordisk-us.com

FDA-2011-P-0482-0001 CP

markets 25 mcg Vagifem®, the Agency must make a determination as to whether 25 mcg Vagifem® was discontinued for a reason related to safety or effectiveness and publish that decision in the Federal Register before it can approve any ANDA.[1] If FDA accepts an ANDA application for 25 mcg Vagifem®, FDA should require the ANDA applicant to include in the labeling for the product information about the availability of and recommendation to begin treatment on the 10 mcg dosage strength of estradiol vaginal tablets. Although Novo Nordisk does not know whether there are any pending ANDAs for either or both strengths of a generic version of Vagifem®, Novo Nordisk submits this Citizen Petition in compliance with FDC Act § 505(q) in the event that such an ANDA exists.

Novo Nordisk acknowledges a Citizen Petition dated January 21, 2005, submitted to FDA by Warner Chilcott (Docket No. FDA-2005-P-0006) requesting that FDA require that an ANDA for generic estradiol vaginal cream be supported by clinical study data. Novo Nordisk submitted a similar Citizen Petition dated February 18, 2009 (Docket No. FDA-2009-P-0089), requesting that FDA not approve any ANDA for a generic version of Vagifem® 25 mcg unless the generic applicant provides data from adequate and well-controlled multiple endpoint clinical trials designed to assess the decrease of vaginal pH, cytologic maturation of the vaginal epithelium and symptom relief. Novo Nordisk also submitted a Citizen Petition dated July 26, 2010 (Docket No. FDA-2010-P-0403) requesting that FDA require any applicant for a generic version of 25 mcg Vagifem® (estradiol vaginal tablets) include in the labeling for the product information about the availability of and recommendation to begin treatment on the 10 mcg dosage strength of estradiol vaginal tablets. FDA has not issued a substantive response to any of the petitions. Novo Nordisk adopts and reiterates many of the same arguments with regard to its request that FDA require that ANDA applicants demonstrate bioequivalence via clinical trials. Because this petition supersedes Citizen Petition FDA-2010-D-0403, Novo Nordisk is withdrawing that petition by letter to that docket.

A. ACTION REQUESTED

Novo Nordisk asks that FDA do the following:

---

[1] FDA has not made a determination as to whether Vagifem® 25 mcg was removed from the market for a reason related to safety or effectiveness. FDA regulations provide that if an ANDA applicant references a listed drug that the sponsor has ceased to market, FDA must determine whether the drug was removed from the market for reasons of safety or effectiveness before the ANDA can be approved. 21 C.F.R. § 314.161(a)(1). If FDA determines that Vagifem® 25 mcg was not withdrawn for safety or effectiveness reasons, the Agency must publish notice of this determination in the Federal Register. *Id.* § 314.161(e). If the Agency has not made such a determination on its own initiative, the ANDA relying on the discontinued drug must be accompanied by a petition asking FDA to determine whether the drug was withdrawn from the market for reasons of safety or effectiveness. *Id.* § 314.122. Novo Nordisk is not aware that any such petition has been submitted to FDA.

(1) Refrain from approving any ANDA for either strength of Vagifem® unless or until the applicant provides data from well-controlled multiple endpoint clinical trials. These trials should be conducted in line with FDA guidelines and should be sufficient to show that the drug is safe and effective and bioequivalent to the comparable dosage strength of Vagifem®.

(2) If FDA determines that Vagifem® 25 mcg was not discontinued for reasons of safety or efficacy, Novo Nordisk asks that the Agency prohibit an applicant for a generic version of Vagifem® 25 mcg from "carving out" language regarding the 10 mcg dosage strength. Specifically, Novo Nordisk asks that FDA require the following language in the labeling for a generic version of Vagifem®:

- "Use of estrogen-alone, or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman." (Section 2:1 of Vagifem® Full Prescribing Information).

- "Generally, women should be started at the 10 mcg dosage strength." (Section 2.2 of Vagifem® Full Prescribing Information).

- Information about Vagifem® 10 mcg that appears in sections 6.1, 11, 12.3, and 14.1 of the Vagifem® Full Prescribing Information as well as in the Highlights of Prescribing Information under the heading "Dosage Forms and Strengths."

B. STATEMENT OF GROUNDS

1. Vagifem® Background

FDA approved Vagifem® 25 mcg in March 1999 (NDA 20-908) for use by women for the relief of symptoms related to postmenopausal atrophic vaginitis due to estrogen deficiency. Vagifem® is a 6 mm tablet administered intravaginally via a patented plastic applicator to provide local estrogen therapy. Once inserted, the tablet adheres to the vaginal wall and dissolves, providing a slow release of estradiol. The dissolved active ingredient then coats the vaginal walls and is absorbed. Once absorbed, the estradiol binds to and activates estrogen receptors in the vagina, which promotes cellular maturation of the vaginal epithelium, increases vaginal secretions and moisture, and normalizes the vaginal pH, all of which contribute to the resolution of the symptoms of vaginal atrophy.

When Vagifem® 25 mcg was first introduced, it was believed that 25 mcg was the necessary dosage for efficacy. However, studies conducted for the Vagifem® 25 mcg approval suggested that a 10 mcg dose might also be effective for women with postmenopausal atrophic vaginitis, so Novo Nordisk conducted a clinical trial to study the efficacy of the 10 mcg dose.

The trial showed that the 10 mcg dose is effective, and FDA approved Vagifem® 10 mcg (sNDA 013) in November 2009 for the same indication as Vagifem® 25 mcg.

As a consequence, Novo Nordisk discontinued the sale of Vagifem® 25 mcg on July 30, 2010, and Vagifem® 25 mcg is listed as discontinued in *Approved Drug Products with Therapeutic Equivalence Evaluations* ("the Orange Book"). FDA has not made a determination whether Vagifem® 25 mcg has been withdrawn for a reason related to safety or efficacy. The expiration date of the final lots of Vagifem® 25 mcg is in 2013, and until then the Vagifem® labeling will continue to reference both the 10 and 25 mcg versions, recommend that treatment begin with the 10 mcg dosage strength of Vagifem®, recommend that women start estrogen therapy at the lowest dose, and provide information on the clinical study used to establish the effectiveness of Vagifem® 10 mcg. The labels for Vagifem® 25 mcg also bear a yellow sticker informing patients that the dose is being discontinued and asking them to contact their healthcare provider or Novo Nordisk for more information.[2] Once the final lot of 25 mcg Vagifem® expires, the labeling for Vagifem® will refer only to the 10 mcg dosage strength. Limited sales of Vagifem® 25 mcg continue as pharmacies exhaust their supplies, but major wholesalers have told Novo Nordisk that their inventories of Vagifem® 25 mcg have been exhausted.

Novo Nordisk conducted 20 clinical trials, including three clinical pharmacology trials, three pharmacokinetic trials and 14 efficacy and safety trials, in the United States, Canada, Europe, and Australia, to support the approval of the Vagifem® products. For each trial, all of the subjects used Novo Nordisk's patented applicator to insert the tablet. Novo Nordisk currently has a method of use patent for Vagifem® 10 mcg for treatment of atrophic vaginitis due to menopause (U-1023).[3]

2. Analysis

a. FDA should not receive or approve an ANDA for generic versions of Vagifem® 25 mcg and/or 10 mcg unless the applicant demonstrates bioequivalence for each dosage strength based on data from adequate and well-controlled multiple endpoint clinical trials.

---

[2] The sticker reads, "Attention! This dose is being discontinued. Please contact your health care provider about an alternate dosing option. For more information, please call Novo Nordisk at 1-866-668-6336 or visit newdosingoption.com." FDA approved this labeling revision on May 17, 2011. *See* Supplemental Approval, Letter to Anne Phillips, Novo Nordisk Pharmaceuticals, Inc. from Scott Monroe, Director, Division of Reproductive and Urologic Products, May 17, 2011.

[3] U.S. Patent No. 7,018,992 (expires Sept. 17, 2022).

FDA should require that an ANDA applicant for generic Vagifem® demonstrate bioequivalence by a well-controlled multiple endpoint clinical trial. Under FDA's existing bioequivalence regulations, the types of evidence that an applicant may use to show bioequivalence, listed "in descending order of accuracy, sensitivity, and reproducibility," are: (1) *in vivo* tests in humans to measure the active ingredient, moiety, or metabolite in "whole blood, plasma, serum, or other appropriate biological fluid," or "[a]n *in vitro* test that has been correlated with and is predictive of human *in vivo* bioavailability data;" (2) an *in vivo* test in humans to measure urinary excretion of the active moiety or metabolite; (3) "[a]n *in vivo* test in humans in which an appropriate acute pharmacological effect of the active moiety" or active metabolite "are measured as a function of time;" (4) a well-controlled clinical trial to "establish the safety and effectiveness of the drug product;" (5) an "*in vitro* test acceptable to FDA;" and (6) "[a]ny other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence."[4]

In vivo (and *in vitro*) tests in human blood, serum, or urine will not provide accurate or reliable data on bioequivalence for a generic Vagifem® product because Vagifem® acts locally within the vagina to treat atrophic vaginitis. The mechanism of action for locally-acting treatments for atrophic vaginitis means that typical routes of metabolism for estrogen are largely bypassed. The very low doses given locally assure that there is minimal systemic absorption of estradiol and concentrations of serum estradiol remain in the menopausal range, so the types of *in vivo* studies typically used to demonstrate the bioequivalence of systemically absorbed drug products are inadequate to demonstrate the bioequivalence of topical estradiol products. Therefore, an applicant seeking approval for a generic version of Vagifem® must demonstrate bioequivalence through an alternative scientifically valid method; namely, in a multiple endpoint clinical study designed to measure the safety and efficacy of the test drug in post-menopausal women with atrophic vaginitis. Efficacy should be measured by the decrease of vaginal pH, cytologic maturation of the vaginal epithelium and patient reports of symptom relief. Such a trial is the only meaningful type of safety and efficacy study that would meet the requirements of FDC Act §§ 505(j)(2)(A) and 505(j)(8)(C), and 21 C.F.R. § 314.94(a).

In addition, FDA should require that any applicant seeking approval for a generic version of Vagifem® conduct a pharmacokinetic study designed as a parallel design bioequivalence study. A crucial aspect of such a study is the dissolution profile of the drug at varying pH levels. Novo Nordisk submitted two pharmacokinetic studies with its original NDA for Vagifem® 25 mcg and one pharmacokinetic study for Vagifem® 10 mcg, including a study of dissolution in a vaginal environment with a pH range of 3.0 to 6.8. The parallel design is important because in a crossover study, treatment from the first estrogen product can affect the efficacy of the second treatment. These studies provided important information about dissolution, and the range of pH is important because vaginal pH varies markedly in this population and decreases as treatment continues. Even though such a study is not, by itself, sufficient for ANDA approval, the pharmacokinetic qualities of estradiol tablets are crucial for the efficacy of the drug and therefore these types of studies should be required for any generic version of Vagifem®.

---

[4] 21 C.F.R. § 320.24(b)(1)-(6) (emphasis added).

Novo Nordisk also requests that FDA require that any applicant seeking approval of an ANDA for a generic version of a locally acting, topical estrogen therapy product conduct a clinical trial in accordance with the Agency's recommendations in the Draft Guidance.[5] Although the Draft Guidance does not specifically address ANDAs, it is appropriate that an ANDA for estradiol vaginal tablets follow the document because of the unique challenges of showing bioequivalence for a locally acting, topical product. The Draft Guidance recommends that sponsors of a drug to treat vaginal atrophy complete at least one randomized, double-blind, 12-week, placebo-controlled clinical trial to support the efficacy of the drug. This should be the standard for a clinical trial to support the approval of a generic version of Vagifem®.

The Draft Guidance further recommends that only postmenopausal women be included in the study and that study participants be women "who have self-identified at least one moderate to severe symptom" of vaginal atrophy "that is the most bothersome to her, have no greater than 5 percent superficial cells on a vaginal smear, and have a vaginal pH > 5.0." Draft Guidance at 3. The co-primary endpoints that the Draft Guidance recommends for vaginal atrophy include mean change from baseline to week 12 of the symptom that is most bothersome to the subject, vaginal pH, and vaginal maturation index (parabasal, intermediate, and superficial cells). It is very important that a generic version of Vagifem® meet these endpoints in order to assure that the generic product is effective for its intended use.

b. FDA should not permit an ANDA applicant for generic Vagifem® 25 mcg to omit language recommending that women take the lowest available dose because doing so would render the drug less safe.

If FDA determines that Vagifem® 25 mcg was not withdrawn for safety or effectiveness reasons, FDA should require any ANDA applicant for generic Vagifem® 25 mcg to use the same labeling as used for Vagifem® 25 mcg and 10 mcg tablets. In particular, FDA should not permit an ANDA applicant to "carve out" the following language from the approved Vagifem® prescribing information:

- "Use of estrogen-alone, or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman." (Section 2:1 of Vagifem® Full Prescribing Information).

- "Generally, women should be started at the 10 mcg dosage strength." (Section 2.2 of Vagifem® Full Prescribing Information).

---

5 Draft Guidance for Industry: Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation, at 2 (January 2003). ("the Draft Guidance").

- Information about Vagifem® 10 mcg that appears in sections 6.1, 11, 12.3, and 14.1 of the Vagifem® Full Prescribing Information as well as in the Highlights of Prescribing Information under the heading "Dosage Forms and Strengths."

FDA regulations permit approval of ANDA labeling that omits certain aspects of the listed drug's approved labeling only if the "aspects of the listed drug's labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use."[6] FDA recently granted a request that the Agency not allow ANDA applicants to carve out dosing information because doing so would render the generic drug less safe than the listed drug. Mutual Pharmaceutical Company, Inc. ("Mutual") asked FDA to prohibit ANDA applicants for generic colchicine products from carving out information on drug-drug interactions, including dosing adjustments needed to prevent toxicity. Mutual had conducted studies of colchicine that found that a lower dose was required when the drug was co-administered with other drugs. Based on that information, FDA recommended that Mutual's colchicine product labeling include lower dosing information, and Mutual argued that this information should not be carved out of any generic drug labeling. FDA agreed with Mutual and determined that the dosing information should be required in any generic drug labeling because excluding the information could jeopardize patient safety.[7] Novo Nordisk believes that, like colchicine, information on the lower dosage of Vagifem® is important for patient health and should not be carved out of the labeling.

Novo Nordisk has a method of use patent and three-year Hatch-Waxman exclusivity for the use of Vagifem® 10 mcg for the treatment of atrophic vaginitis due to menopause. An ANDA applicant for a 25 mcg dosage strength product may seek to omit the above-mentioned language if the applicant does not seek approval for a 10 mcg dosage strength product. However, omitting this language would be contrary to the current recommended dosing approved by FDA for estradiol vaginal tablets as well as the dosing recommended by the medical community, and therefore could render the generic product less safe than Vagifem®.

Omitting information on the 10 mcg strength would also be contrary to FDA's own recommendations. FDA requires the labeling for hormone therapy products, including Vagifem®, to bear black box warnings related to the risks of estrogen and progestin therapy and recommendations that prescribers start patients on the lowest effective dose. FDA also published a draft guidance document for sponsors recommending that they "develop the lowest doses and exposures for both estrogens and progestins for indications sought" and "investigate dosing schedules and drug delivery systems that can achieve efficacy with the lowest possible exposure."

---

6 21 C.F.R. § 314.127(a)(7).

7 FDA response to FDA Docket No. 2010-P-0614, May 25, 2011.

Draft Guidance at 2. FDA uses its website to recommend to women directly that they should use estrogens and progestins "at the lowest doses for the shortest duration to reach treatment goals."[8]

The current recommendation for women considering hormone therapy is that they should generally start treatment with the lowest dosage strength available. If information about dosing and the availability of a 10 mcg strength is omitted from generic labeling, some prescribers may not be aware that a lower strength is available, potentially exposing some women to higher dosages of estradiol than necessary. Permitting an ANDA applicant to carve out language about the availability of the 10 mcg dosage strength, as well as the recommendations that women generally begin treatment on the lowest dosage strength, could have a negative impact on women's health and would render the generic product less safe than Vagifem®.

C. CONCLUSION

Prior to approving an ANDA for a generic version of Vagifem® 25 mcg, FDA must make a determination as to whether the drug was discontinued for a reason related to safety or effectiveness. Moreover, Novo Nordisk respectfully requests that FDA not receive or approve any ANDAs for generic Vagifem® 10 mcg or 25 mcg without bioequivalence data from clinical trials because a clinical trial is the only reliable way to demonstrate bioequivalence for a locally-acting product like Vagifem®.

Novo Nordisk also requests that FDA not approve any generic Vagifem® product unless the labeling includes information on the 10 mcg strength and a recommendation that women generally begin treatment with the lowest dosage strength. The current recommendation on the use of estrogen and progestin therapy is that women should use the lowest effective dose available, so it is important that women have information about the availability of the 10 mcg dosage strength.

D. ENVIRONMENTAL IMPACT

A claim for categorical exclusion from the requirements for an Environmental Assessment is made under 21 C.F.R. § 25.31(a).

E. ECONOMIC IMPACT

An economic impact statement will be submitted at the request of the Commissioner.

---

8 *See* Questions and Answers for Estrogen and Estrogen with Progestin Therapies for Postmenopausal Women (Updated), *available at* http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135339.htm.

F. CERTIFICATION

Pursuant to FDC Act § 505(q), I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: January 1, 1989 (information on the properties of Vagifem® 25 mcg); May 24, 2007 (information on the properties of Vagifem® 10 mcg). If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: none, other than my normal compensation as a Novo Nordisk employee. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

Jeremy Berger
Senior Litigation Attorney
Novo Nordisk Inc.

cc: Keith O. Webber, Ph.D., Acting Director
Office of Generic Drugs
CDER, FDA