WARNING LETTER

Metuchen Pharmaceuticals, LLC.

MARCS-CMS 590713 — AUGUST 16, 2019

Product:

Drugs

Recipient:

Greg Ford

President and Chief Executive Officer

Metuchen Pharmaceuticals, LLC.

4400 Route 9 South, Suite 1000
Freehold, NJ 07728
United States

Issuing Office:

Center for Drug Evaluation and Research

10903 New Hampshire Avenue
Silver Spring, MD 20993
United States

RE: NDA 202276
STENDRA® (avanafil) tablets, for oral use
MA 169, 182, 187

WARNING LETTER

Dear Mr. Ford:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a direct-to-consumer print ad (STEN-MET-28), and Display Banners STEN-MET-02 (banners "02")***1*** and STEN-MET-06 (banners "06") (collectively banners) for STENDRA® (avanafil) tablets, for oral use (Stendra) submitted by or on behalf of Metuchen Pharmaceuticals, LLC (Metuchen)***2*** under cover of Form FDA 2253. The print ad and banners make false or misleading claims and/or representations about the risks associated with and efficacy of Stendra. Thus, the print ad and banners misbrand Stendra within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act) and make its distribution violative. 21 U.S.C. 352(a) & (n); 321(n), 331(a). See 21 CFR 202.1(e)(3)(ii), (iii); (e)(5); (e)(7)(viii). The print ad also provides evidence that Stendra is intended for a new use for which it lacks approval, and for which its labeling does not provide adequate directions for use, which also renders Stendra misbranded or otherwise makes its distribution violative. 21 U.S.C. 352(f)(1); 331(a); see 21 CFR 201.5; 201.100; 201.115; 201.128. These violations are

concerning from a public health perspective because they create a misleading impression about the safety and effectiveness of Stendra and suggest a use for which the labeling does not provide adequate directions for safe and effective use of the product.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Stendra.***3*** According to the FDA-approved product labeling (PI):

STENDRA is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of erectile dysfunction.

Stendra is contraindicated with any form of organic nitrates, in patients with known hypersensitivity to any component of the tablet, and in patients who are using a guanylate cyclase stimulator. The PI for Stendra includes warnings and precautions regarding cardiovascular risks, concomitant use of CYP3A4 inhibitors, prolonged erection, effects on eye, sudden hearing loss, alpha-blockers and other antihypertensives, alcohol, combination with other PDE5 inhibitors or erectile dysfunction therapies, effects on bleeding, and counseling patients about sexually transmitted diseases. The most common adverse reactions reported with use of Stendra include headache, flushing, nasal congestion, nasopharyngitis, and back pain.

Lack of Adequate Directions for Use

The print ad includes the following headline claim (emphasis original):

• "Treat ED and Reduce Risk of Heart Failure with a PDE-5 Inhibitor[.]"

This claim provides evidence that Stendra is intended for a new use for which it lacks approval, and for which its labeling does not provide adequate directions for use. Stendra is not approved for reducing the risk of heart failure, and its labeling does not contain adequate directions for such use, thereby rendering the drug misbranded. This claim, which misleadingly suggests that Stendra is safe and effective for a use for which it is not approved and for which you have provided no evidence to support, is especially concerning from a public health perspective given that the PI contains a warning and precaution regarding cardiovascular risks, and specifically states that Stendra is not recommended for patients with New York Heart Association Class 2 or greater congestive heart failure.

False or Misleading Risk Presentations

Promotional materials misbrand a drug if they are false or misleading with respect to risk. The determination of whether promotional materials are misleading includes, among other things, not only representations made or suggested in promotional materials, but also failure to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials.

The print ad and banners are misleading because they include claims and/or representations about the uses and/or benefits of Stendra, but fail to include important risk information associated with the drug as described below:

Banners "06"

The banners "06" include the claims, "**Get Hard & Stay Hard[,]**" (emphasis original) and, "Indulge in life's sweetest pleasures whenever you want[,]" yet fail to communicate any risk information about the product. These presentations create a misleading impression about the product's safety, which is further exacerbated by the efficacy claim, "**Get Hard & Stay Hard[,]**" when there is a warning and precaution regarding prolonged erection, which can result in irreversible damage to the erectile tissue.

Banners "02"

The banners "02" include the following claims (emphasis original):

Version A
o "**The ED Pill For Your Lifestyle[.]**"
o "Stendra prescriptions can be taken with or without food and alcohol."
Version B
o "**The Fast-Acting ED Prescription[.]**"
o "Stendra can be effective in as little as 15 minutes, with or without food."

Although the banners "02" include the statement, "Common side effects include: headache, flushing, and nasal congestion," they fail to include any of the contraindications or warnings and precautions of the drug, creating a misleading impression about the safety of Stendra. This misleading impression is further exacerbated by claiming in banner "02" Version A that, "Stendra prescriptions can be taken with or without food and alcohol[,]" while failing to disclose that there is a specific risk related to drinking too much alcohol when taking Stendra which can increase patients' chances of headache, dizziness, increased heart rate, or lowered blood pressure.

We acknowledge that the Clinical Studies section of the PI states that food and alcohol intake was not restricted during the studies. However, this does not mitigate the omission of material information regarding the risk of alcohol use with Stendra as described in the Warnings and Precautions and Patient Counseling Information sections of the PI and in the Patient Information.

Print ad

The print ad includes several efficacy claims for Stendra, as well as a statement communicating the warning and precaution regarding alcohol and most common side effects of Stendra. However, the print ad fails to disclose any of the contraindications or other warnings and precautions associated with the product.

By omitting risks associated with Stendra, the banners and print ad fail to provide material information about the consequences that may result from the use of the drug and create a misleading impression about the drug's safety. These misleading presentations are especially problematic from a public health perspective due to the multiple serious risks associated with the drug.

We acknowledge that the banners and print ad include the statements, "Ask your doctor for more information[,]" (capitalized emphasis omitted) and, "Learn more at BIT.LY/STENDRA[,]" respectively. However, these statements do not mitigate the misleading impressions regarding Stendra's safety created by the omission of risk information from the banners and print ad.

Banners "06"

The banners "06" make the following claim about the use of Stendra:

• "Indulge in life's sweetest pleasures whenever you want."

This claim is misleading because it suggests that Stendra can safely be dosed to provide efficacy at any timepoint (i.e. "whenever you want"), when this is not the case. The PI for Stendra states, "The maximum recommended dosing frequency is once per day" because the totality of the clinical experience during product development was not adequate to support safety of a Stendra regimen that included more than one dose per day. Additionally, the duration of Stendra's effect is inconclusive. The development program for Stendra evaluated the efficacy of the drug between 15 minutes and 2 hours of dosing. Data points beyond 2 hours of dosing were too few to support meaningful efficacy conclusions. Therefore, given that the PI recommends a maximum dosing frequency of once a day and that efficacy beyond 2 hours after administration is inconclusive, the claim that Stendra is effective "whenever" a patient wants is misleading. FDA is not aware of data to support Stendra's efficacy outside of 15 minutes to 2 hours after dosing. If you have data to support this claim, please submit them to FDA for review.

Print ad

The print ad***4*** includes the following claims (bolded emphasis original, underlined emphasis added):

• "**Treat ED and Reduce Risk of Heart Failure with a PDE-5 Inhibitor[.]**"
• "Stendra (Avanafil) is . . . safe and effective for those with heart disease . . . ."

These claims are false or misleading because they suggest that Stendra is safe for all patients with heart disease, including all patients with heart failure. While there is evidence that PDE-5 inhibitors, including Stendra, may be safe and effective for men with **some** types of heart disease, the PI for Stendra contains a warning and precaution for cardiovascular risks associated with the drug. These risks include avoiding use of Stendra in men for whom sexual activity is inadvisable because of their underlying cardiovascular status, the particular sensitivity to the actions of Stendra of patients with left ventricular outflow obstruction or severely impaired autonomic control of blood pressure, and the potential for Stendra to augment the blood pressure-lowering effect of other anti-hypertensive medications, such as alpha-blockers, which may lead to hypotension. Moreover, the Warnings and Precautions section of the PI states:

The following groups of patients were not included in clinical safety and efficacy trials for STENDRA, and therefore until further information is available, STENDRA is not recommended for the following groups:

• Patients who have suffered a myocardial infarction, stroke, life-threatening arrhythmia, or coronary revascularization within the last 6 months;
• Patients with resting hypotension (blood pressure less than 90/50 mmHg) or hypertension (blood pressure greater than 170/100 mmHg);
• Patients with unstable angina, angina with sexual intercourse, or New York Heart Association Class 2 or greater congestive heart failure.

In addition, the print ad includes the following claim (bolded emphasis original, underlined emphasis added):

• "**Stendra is the next-generation, PDE-5 inhibitor that improves erectile function**."

This claim is misleading because it suggests that by being, "[T]he next-generation, PDE-5 inhibitor," Stendra is safer or more effective than its competitors. No references were cited in support of this claim and we are not aware of evidence to support the suggestion that Stendra is safer or more effective than its competitors. If you have data to support this claim, please submit them to FDA for review.

Promotional materials are also misleading if they fail to present information about risks associated with a drug with a prominence and readability reasonably comparable with the presentation of information related to the effectiveness of the drug. Factors impacting prominence and readability include typography, layout, contrast, headlines, paragraphing, white space, and other techniques apt to achieve emphasis. The print ad prominently presents efficacy claims in large, bolded font size and colorful text and graphics surrounded by a significant amount of white space. In contrast, the limited risk information is presented in much smaller font size, surrounded by little white space, and in single-spaced format at the bottom of the ad. As such, the print ad fails to present the risk information with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of the drug, thus further minimizing the risks associated with Stendra.

False or Misleading Claims about Efficacy

The banners "06" make the following representations about the use of Stendra (bold emphasis original):

• "**Get Hard & Stay Hard**"
• "Indulge in life's sweetest pleasures whenever you want."

The banners "06" are misleading because they fail to communicate material information regarding the indication for Stendra. Specifically, they omit the following material information from the INDICATIONS AND USAGE section of the PI (underlined emphasis added):

> Stendra is a phosphodiesterase 5 (PDE5) inhibitor indicated **for the treatment of erectile dysfunction**.

By omitting this information, the banners "06" create a misleading impression about the indication for Stendra. Specifically, they create the misleading impression that Stendra has been demonstrated to be safe and effective as an aid to achieve and maintain an erection for people other than those with the medical condition of erectile dysfunction (ED). The omission of the indication is particularly concerning from a public health perspective due to the serious health risks associated with Stendra.

Conclusion and Requested Action

For the reasons discussed above, the print ad and banners misbrand Stendra within the meaning of the FD&C Act and makes its distribution violative. 21 U.S.C. 352(a) & (n); 321(n), 331(a). See 21 CFR 202.1(e)(3)(ii), (iii); (e)(5); (e)(7)(viii). The print ad also provides evidence that Stendra is intended for a new use for which it lacks approval, and for which its labeling does not provide adequate directions for use, which also renders Stendra misbranded or otherwise makes its distribution violative. 21 U.S.C. 352(f)(1); 331(a); see 21 CFR 201.5; 201.100; 201.115; 201.128.

OPDP requests that Metuchen immediately cease misbranding Stendra and/or cease introducing the misbranded drug into interstate commerce. Please submit a written response to this letter on or before August 30, 2019, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Stendra that contain representations such as those described above, and explaining your plan for discontinuing use of such materials, or, in the alternative, for ceasing distribution of Stendra. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. In order to clearly identify the violative promotional piece(s) and/or activity and focus on the corrective message(s), OPDP recommends that corrective piece(s) include a description of the violative promotional

piece(s) and/or activity, include a summary of the violative message(s), provide information to correct each of the violative message(s), and be free of promotional claims and presentations. To the extent possible, corrective messaging should be distributed using the same media, and generally for the same duration of time and with the same frequency that the violative promotional material was disseminated. If you believe that your products are not in violation of the FD&C Act, include your reasoning and any supporting information for our consideration.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266.** A courtesy copy can be sent by facsimile to (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA 169, 182, and 187 in addition to the NDA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Warning Letter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Stendra comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,
{See appended electronic signature page}
Robert Dean
Director
Division of Advertising & Promotion Review 2
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ROBERT T DEAN
08/16/2019 10:03:47 AM

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1 Specifically, we refer to the Display Banners identified in the submission as “Product Claim” banners.

2 The banners were submitted under cover of Form FDA 2253 by Mist Pharmaceuticals, LLC, as a U.S. agent of Metuchen Pharmaceuticals, LLC. The print ad was submitted under cover of Form FDA 2253 by Metuchen Pharmaceuticals, LLC.

3 This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional pieces cited in this letter.

4 According to the information you provided under cover of Form FDA 2253, "This print ad will be shown in CardioSmart magazine, distributed by the American College of Cardiology to the magazine's subscribers."

PROMOTIONAL MATERIALS (/media/130383/download)

More Warning Letters (/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters)