DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Leland F. Wilson
President and Chief Executive Officer
VIVUS, Inc.
1172 Castro Street
Mountain View, CA 94040

RE: NDA # 20-700
MUSE® (alprostadil) Urethral Suppository
MACMIS ID # 12039

WARNING LETTER

Dear Mr. Wilson:

The Division of Drug Marketing, Advertising, and Communications (DDMAC), in consultation with the Division of Reproductive and Urologic Drug Products, has reviewed a 30-second direct-to-consumer (DTC) television advertisement (TV ad) (Admis #146228) for MUSE® (alprostadil) Urethral Suppository submitted by VIVUS, Inc. (VIVUS) under cover of Form FDA 2253 and a website promoting MUSE that is maintained by or on behalf of VIVUS (http://www.VIVUS.com). The TV ad omits and minimizes risk information, fails adequately to disclose a material fact, makes unsubstantiated effectiveness claims, and fails to make adequate provision for dissemination of the FDA-approved professional labeling (PI) for MUSE. The website minimizes risk information and makes unsubstantiated effectiveness claims. The TV ad and website are, therefore, in violation of the Federal Food, Drug, and Cosmetic Act (Act) and FDA implementing regulations. See 21 U.S.C. 321(n), 352(a) & (n); 21 C.F.R. 202.1(e). Additionally, VIVUS failed to submit the website accompanied by a completed transmittal Form FDA 2253 as required by 21 C.F.R. 314.81(b)(3)(i).

Background

MUSE is a trans-urethral system for the delivery of alprostadil to the male urethra. It is indicated for the treatment of erectile dysfunction (ED). The contraindications section of the PI states that MUSE is contraindicated in men who have "…abnormal penile anatomy…sickle cell anemia or trait, thrombocythemia, polycythemia, [or] multiple myeloma…." The contraindications section further states: "MUSE should not be used in men for whom sexual activity is inadvisable…" and "MUSE should not be used for sexual intercourse with a pregnant woman unless the couple uses a condom barrier." The warnings section of the PI states that there is a "potential for symptomatic hypotension and syncope [fainting], which occurred in 3% and 0.4%, respectively….During post-marketing

surveillance syncope occurring within one hour of administration has been reported. Patients should be cautioned to avoid activities, such as driving or hazardous tasks, where injury could result if hypotension or syncope were to occur after MUSE administration." The precautions section of the PI states: "Sexual intercourse is considered a vigorous physical activity, and it increases heart rate as well as cardiac work. Physicians may want to examine the cardiac fitness of patients prior to treating erectile dysfunction."

Omission of Risk Information

The TV ad omits the fact that MUSE is contraindicated in men for whom sexual activity is inadvisable due to cardiac problems. The TV ad also omits the warning regarding symptomatic hypotension and syncope following insertion of MUSE. This contraindication and warning describe some of the most serious risks associated with MUSE. See 21 C.F.R. 202.1(e)(1).

Minimization of Risk Information

TV Ad

The TV ad is misleading because it minimizes the risks of MUSE both in men with abnormal penile anatomy and in men who are at increased risk for priapism because of venous thrombosis or a hyperviscosity syndrome. Specifically, the voiceover (VO) states "Do not use if you…have abnormal anatomy or some blood disorders…" (emphasis added). The term "abnormal anatomy" is inadequate to describe the specific part of the body which cannot be abnormal. This contraindication is described in the PI as "abnormal penile anatomy" and in the PPI as "an abnormally formed penis." Furthermore, the term "blood disorders" is inadequate to describe the wide range of conditions listed in the contraindications section of the PI, specifically, "sickle cell anemia or trait, thrombocythemia, polycythemia, [and] multiple myeloma." See 21 C.F.R. 202.1(e)(6)(xx).

Website

The section of the VIVUS website that describes MUSE (http://www.VIVUS.com/fr_set.asp?SECTION=museouter) begins with a page containing two headers. Under the first header, "MUSE Product Resources Index," there are 13 "links for information about MUSE." Under the second header, "What is MUSE?" there is information about the indication, dosage, and usage of MUSE. This section contains several effectiveness claims without any risk information disclosures relative to the benefit information.

Although the risk information is available in certain areas of the website, there is no signal that the links will lead the reader to this information. Only one of the links under "MUSE Product Resources Index," the "Patient Package Insert" link (which contains the FDA-approved patient labeling (PPI)), hints to risk information up front because it "explains in detail MUSE administration, and related precautions." However, the term "related precautions" in this presentation does not adequately communicate that MUSE is associated with serious risks such as those described in the contraindications and warnings sections of the PI.

The "patient instruction video" on the website minimizes the risk of symptomatic hypotension (decreased blood pressure) and syncope (fainting). The video makes the following VO statement, with concurrent on screen text (SUPER):

- "Decreases in blood pressure and fainting were rarely reported in clinical studies—3% and 0.4%, respectively. It only occurred during initial in-office dosing" (VO)
- "3% decreased blood pressure, 0.4% fainted" (SUPER)
- "Initial in-office dosing only" (SUPER)

The video is misleading because it suggests that symptomatic hypotension and syncope will occur only during "initial in-office dosing." According to the warnings section of the PI, "During post-marketing surveillance syncope occurring within one hour of administration has been reported. Patients should be cautioned to avoid activities, such as driving or hazardous tasks, where injury could result if hypotension or syncope were to occur after MUSE administration."

Failure Adequately to Disclose Material Fact

The TV ad fails adequately to disclose the method of administration of MUSE. This is a material fact about the product within the meaning of section 201(n) of the Act, 21 U.S.C. 321(n). The method of administration is also pertinent to the ad's comparative claims to other ED treatments that are available as oral tablets. The only hint that this product is a combination of a device and a medicated pellet to be inserted manually into the opening of the man's glans is the phrase "urethral suppository" in the product's logo, which appears in poor contrast on screen at the end of the ad. In an untitled letter, dated April 1, 1998, DDMAC objected to another DTC broadcast ad for MUSE that omitted the fact that MUSE is a suppository inserted into the male urethra. In that letter, DDMAC stated that "'urethral suppository' [is] an unfamiliar medical term that does not communicate this product characteristic…" and "the majority of men exposed to this advertisement will not understand that MUSE is a suppository designed to be inserted into the opening of a man's penis…." We note that your April 14, 1998, letter (responding to our April 1, 1998, untitled letter) states "…the term 'urethral suppository' has been clarified with the statement 'MUSE is applied into the urinary opening' to communicate this product characteristic to the average consumer." We did not object to this proposed language in our May 18, 1998, advisory letter regarding proposed DTC print ads that you submitted on April 29, 1998.

Unsubstantiated Effectiveness Claims

TV Ad

The TV ad makes unsubstantiated claims that MUSE is superior to other ED products. The TV ad VO states "Just like you, I've tried many products. Nothing worked for me until I tried MUSE" and "[MUSE] works in about 10 minutes, not an hour." These claims suggest that MUSE is useful in patients who are refractory to other ED treatments, is more effective in treating ED than other treatments, and has a faster onset of action than other medications. FDA is not aware of substantial evidence or substantial clinical experience supporting such claims. If you have data to support such claims, please submit them to FDA for review.

Website

The website pages "Radical Prostatectomy & Oxygenation," "'Radical Prostatectomy' Brochure," and "MUSE & Diabetes" contain claims about the use of MUSE in diabetes and radical prostatectomy patients. We are not aware of substantial evidence or substantial clinical experience to support these claims. If you have data to support such claims, please submit them to FDA for review.

The "patient instruction video" on the website claims that MUSE will provide "a more normal and spontaneous sexual lifestyle" and "allow[s] the spontaneity that you and your sexual partner desire." This claim is misleading because it implies an outcome from treatment with MUSE that was not measured in clinical trials and is not supported with substantial evidence or substantial clinical experience. In addition, it is misleading to claim that MUSE will provide a "more normal and spontaneous sexual lifestyle" or "allow the spontaneity that you and your sexual partner desire," when patients must follow at least 12 distinct steps to administer MUSE correctly (as presented in the "How to Administer MUSE" section of the PPI), including inspecting the MUSE system, inserting the suppository into the penis, manually distributing the medication, and waiting approximately 5 to 10 minutes for erection to occur. Because of these complex and time-consuming steps, claims that MUSE increases "spontaneity" or provides "a more normal and spontaneous sexual lifestyle" are false or misleading.

Failure to Make Adequate Provision

The prescription drug advertising regulations provide that a broadcast ads must "contain a brief summary of all necessary information related to side effects and contraindications," or alternatively, "include information relating to the major side effects and contraindications" and make "adequate provision… for dissemination of the approved or permitted package labeling in connection with the broadcast presentation." See 21 C.F.R. 202.1(e)(1). The TV ad does not contain a brief summary. Consequently, the TV ad must include the specified risk information and make adequate provision for dissemination of the PI in connection with the ad.

According to FDA's 1999 "Guidance for Industry on Consumer-Directed Broadcast Advertisements" for prescription drugs, the "adequate provision" requirement envisions an approach to dissemination that will allow most of a potentially diverse audience of consumers with different levels of mobility, different levels of access to technology, different sensitivity to privacy, and different information-seeking styles to have reasonably convenient access to the PI. This broad audience will include, among others, persons who are uncomfortable directly requesting additional prescription drug product information from their healthcare providers, persons without access to computers and the Internet, persons who are uncomfortable actively requesting additional product information about a specific prescription drug by telephone, and persons concerned about providing phone numbers or other personal information in connection with their requests.

The methods provided in the TV ad do not address these significant populations (e.g., by referring to a concurrent print ad or product brochures available at a variety of publicly accessible sites). The TV ad VO states "Talk to your doctor today about MUSE" and the concurrent SUPER reads "Call 1 800 835 9021 for more information or visit www.VIVUS.com for a doctor in your area." The TV ad thus does not satisfy the "adequate provision" requirement.

The Guidance contains suggested mechanisms for reaching passive and privacy-sensitive information seekers, and those without access to technology. The Guidance suggests as possible mechanisms that brochures containing the required information be made available in a variety of public places such as libraries, pharmacies and grocery stores, or a reference in the broadcast ad be made to concurrent print ads containing a means to access the necessary risk information (e.g., toll-free telephone number and address) in publications reaching the exposed audience. These methods, of course, are not exclusive, and you may utilize other methods, as long as the totality of the mechanisms provided ensure that most of the audience exposed to the TV ad will have ready access to the required risk information.

Failure to Submit Under Form FDA 2253

FDA has not received a submission of the website accompanied by a completed transmittal Form FDA 2253, as required by 21 C.F.R. 314.81(b)(3)(i).

Conclusions and Requested Actions

The TV ad and website misbrand MUSE in violation of the Act. Moreover, the website was not submitted to DDMAC at the time of initial dissemination, as required by 21 C.F.R. 314.81(b)(3)(i).

DDMAC requests that VIVUS immediately cease the dissemination of violative promotional materials for MUSE such as those described above. Please submit a written response to this letter on or before June 9, 2004, stating whether you intend to comply with this request, listing all violative promotional materials for MUSE such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a plan of action to disseminate truthful, non-misleading, and complete information to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Room 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857, facsimile at 301-594-6759. In all future correspondence regarding this matter, please refer to MACMIS ID # 12039 in addition to the NDA number. We remind 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 MUSE comply with each applicable requirement of the 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}

Thomas W. Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications

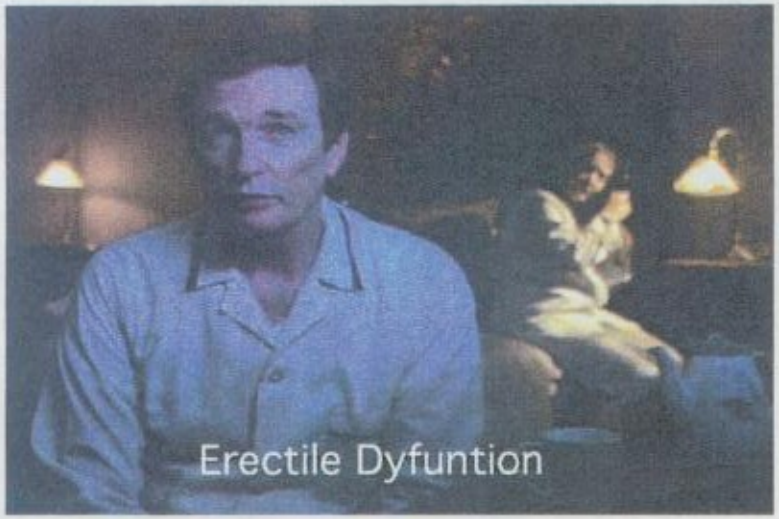
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Abrams

5/25/04 11:47:43 AM

MUSE TV Ad
30secs
English



1. (Man) Do you have a problem in the bedroom? ED?

2. (Man) You are not alone. Just like you I have tried many products. Nothing works for me until I tried Muse.

MUSE TV Ad
30secs
English

3. (Man) Muse helps me to achieve what's important for me and my partner...

(supers) MUSE is an FDA approved product for the treatment of erectile dyfunction.

4. (Man) ... and it works in about 10 minutes, not an hour. Talk to your doctor about Muse because life is about choices.

MUSE TV Ad
30secs
English

5. (Female VO) Side effects can include penile pain and dizziness. Do not use if you are sensitive to alprostadil...

(supers) Talk to your doctor about MUSE.

6. (Female VO) ....have abnormal anatomy or some blood disorder.

MUSE TV Ad
30secs
English

7. (Female VO) Do not use for intercourse with a pregnant woman unless a condom is used.

(supers) Call 1800 835 9021 for more information or visit www.VIVUS.com for a doctor in your area.

8. (Female VO) Talk to your doctor today about Muse.

(supers) Call 1800 835 9021 for more information or visit www.VIVUS.com for a doctor in your area.

MUSE logo.