DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Eric White
Senior Vice President Regulatory Affairs & Quality Assurance
Mission Pharmacal Company
10999 Interstate Highway 10 West, Suite 1000
San Antonio, TX 78230-1355

RE: NDA #021618
Tindamax® (tinidazole) tablets for oral use
MA #45

Dear Mr. White:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a professional sales sheet (TM-112 Rev 1211) (sales sheet) for Tindamax® (tinidazole) tablets for oral use (Tindamax) submitted by Mission Pharmacal Company (Mission) under cover of Form FDA 2253. The sales sheet is false or misleading because it omits risk information, suggests that the drug is useful in a broader range of patients or conditions than has been substantiated for Tindamax, makes unsubstantiated superiority claims, omits material facts, and makes an unsubstantiated claim. Thus, the sales sheet misbrands Tindamax within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and makes its distribution violative of the FD&C Act. 21 U.S.C. 352(a); 321(n); 331(a); 21 CFR 1.21(a). *Cf*. 21 CFR 202.1(e)(5)(i), (iii); (e)(6)(i), (ii); (e)(7)(i). The sales sheet also provides evidence that Tindamax 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 Tindamax misbranded or otherwise makes its distribution violative. *See* 21 U.S.C. 355(a); 352(f); 331(a), (d); 21 CFR 201.5; 201.100; 201.115.

Background

Below are the indication (in pertinent part) and summary of the most serious and most common risks associated with the use of Tindamax.[1]

Tindamax is indicated for the treatment of trichomoniasis caused by *Trichomonas vaginalis.* The organism should be identified by appropriate diagnostic procedures. Because trichomoniasis is a sexually transmitted disease with potentially serious sequelae, partners of infected patients should be treated simultaneously in order to prevent re-infection.

Tindamax is also indicated for the treatment of bacterial vaginosis (BV) in non-pregnant women; pathogens such as *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Candida albicans*, and *Herpes simplex* virus should be ruled out.

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

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Tindamax and other antibacterial drugs, Tindamax should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

The FDA-approved product labeling (PI) for Tindamax contains a Boxed Warning for the potential risk for carcinogenicity, as well as contraindications for use in patients with previous hypersensitivity to tinidazole or other nitroimidazole derivatives, during the first trimester of pregnancy, and in nursing mothers. The PI also contains Warnings and Precautions regarding neurological adverse reactions, vaginal candidiasis, blood dyscrasia, and drug resistance.

In addition, the most common adverse reactions observed with Tindamax include metallic/bitter taste, nausea, weakness/fatigue/malaise, dyspepsia/cramps/epigastric discomfort, vomiting, anorexia, headache, dizziness, and constipation.

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials.

The sales sheet presents efficacy claims and presentations regarding the use of Tindamax for BV and trichomoniasis infections. However, while some risk information is included, the sales sheet fails to reveal any of the contraindications for use of Tindamax and the warnings and precautions regarding neurological adverse reactions and blood dyscrasias associated with the drug. The sales sheet also fails to disclose the common adverse reactions associated with the use of Tindamax. We note the statement, “Please see attached Full Prescribing Information, including Boxed Warning,” and the full Boxed Warning on the bottom of the front page of the sales sheet; however, this does not mitigate the omission of the aforementioned risk information. By omitting serious and common risks associated with the drug, the sales sheet misleadingly suggests that Tindamax is safer than has been demonstrated.

Broadening of Patient Population or Condition

Promotional materials are misleading if they suggest that a drug is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience.

The sales sheet discusses the use of Tindamax for the treatment of BV, but fails to present the drug’s full approved indication. For example, the following claims (bolded emphasis original) are presented:

- “For short, affordable treatment of bacterial vaginosis (BV)…”

- "**TINDAMAX® (tinidazole tablets) is the one and only treatment for BV that gives your patients…**"

This presentation misleadingly broadens Tindamax's patient population or condition. As described in the INDICATIONS AND USAGE section of the PI, "Tinidazole is indicated for the treatment of bacterial vaginosis in non-pregnant women" (emphasis added). Therefore, the sales sheet misleadingly broadens the patient population or condition of Tindamax by suggesting that it is approved for the treatment of BV in all women, including those that may be pregnant, when this is not supported by substantial evidence or substantial clinical experience. This misleading presentation is especially concerning as the sales sheet includes images of women of child-bearing age and omits the drug's contraindication related to use in pregnant women. Information sufficient to support use in the broader patient population or condition suggested in this sales sheet has not been submitted to FDA in an application, nor are we otherwise aware of substantial evidence or substantial clinical experience that would support it. The presentation in the sales sheet also provides evidence that Tindamax is intended for a new use for which it lacks approval, and for which its labeling does not provide adequate directions for use.

Unsubstantiated Superiority Claims

Promotional materials are misleading if they contain a drug comparison that represents or suggests that a drug is safer or more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience.

The sales sheet presents the following claims (bolded emphasis original; underlined emphasis added):

- "**TINDAMAX® (tinidazole tablets) is the one and only treatment for BV that gives your patients** . . .
  - **better tolerability** - than metronidazole, with minimal risk of GI side effects[2],[3],[4]"

These claims misleadingly suggest that Tindamax is superior to metronidazole in the treatment of BV based on its risk profile, when this is not supported by substantial evidence or substantial clinical experience. There are several references cited in support of these claims[2,3,4]. The sponsor's data on file[2] includes studies that observed adverse reactions reported in subjects treated with tinidazole or metronidazole for the treatment of trichomoniasis. The Dickey LJ, et al.[3] article only references information from the Fung HG, et al.[4] article, which was an information search that cited and discussed three additional studies[5,6,7]. These studies reported gastrointestinal adverse reactions in subjects treated

[2] Data on File. Mission Pharmacal Company.
[3] Dickey LJ, Nailor MD, Sobel JD. Guidelines for the treatment of bacterial vaginosis: focus on tinidazole. *Ther Clin Risk Manage*. 2009;5:485-489.
[4] Fung HG, Doan T-L. Tinidazole: a nitromidazole antiprotozoal agent. *Clin Ther*. 2005;27(12)1859-1884.
[5] Kundu SC, Bhattacherjee-I-D, Dasgupta DP, et al. Comparative evaluation of tinidazole and metronidazole in the treatment of amoebic liver abscess. J Indian MedAssoc. 1977;127-129.
[6] Misra NP. A comparative study of tinidazole and metronidazole as a single daily dose for three days in symptomatic intestinal amoebiasis. Drugs. 1978;15(Suppl 1):19-22.

with tinidazole or metronidazole in the treatment of amebic liver abscesses, intestinal amebiasis, and hepatic amebiasis. However, none of the cited references observed BV patients and they did not use the FDA-approved dosing regimens of Tindamax for BV (i.e., 2 g once daily for 2 days or 1 g once daily for 5 days). The claims cited above must be supported by adequate and well-controlled head-to-head clinical trials comparing appropriate doses and dose regimens of your drug and the comparator drug or drugs. Therefore, the references cited do not support the suggestion that Tindamax is superior to metronidazole in the treatment of BV based on the drug's risk profile.

The sales sheet presents the claim, "**shorter dosing** – 2-day or 5-day options streamline recovery vs 7-day metronidazole therapy" (bolded emphasis original; underlined emphasis added). This claim misleadingly suggests that recovery from BV will be easier and/or quicker with Tindamax therapy as compared to metronidazole therapy. We are not aware of substantial evidence to support the claim that Tindamax is associated with easier and/or quicker recovery as compared to metronidazole. We acknowledge that the 2-day or 5-day dosing options for Tindamax are shorter in duration than the indicated regimen of 7-days with metronidazole; however, this does not support the implication that Tindamax "streamlines recovery" from BV. If you have data to support this claim please submit them to FDA for review.

The sales sheet presents the following claims (bolded emphasis original; underlined emphasis added):

- "**TINDAMAX® (tinidazole tablets) is the one and only treatment for BV that gives your patients** . . .
    - **targeted efficacy** - with lower risk of secondary candidiasis infection (4.7%)[8]"

These claims, in conjunction with the presentations cited above that make comparisons to metronidazole, misleadingly suggest that patients on Tindamax have a lower rate of vaginal candidiasis as compared to metronidazole, when this is not supported by substantial evidence. We are not aware of any adequate, well-controlled head-to-head clinical trials demonstrating that Tindamax has a lower rate of vaginal candidiasis as compared to metronidazole. We note that the PI is cited in support of this claim. While vaginal candidiasis is included in the WARNINGS AND PRECAUTIONS section of the PI, there is no information included in the PI to support a decreased risk of secondary candidiasis compared to other therapies. Therefore, the suggestion that Tindamax has a lower rate of vaginal candidiasis as compared to metronidazole is not supported by substantial evidence. If you have data to support these claims, please submit them to FDA for review.

Omission of Material Facts

The sales sheet includes the following claim regarding Tindamax use for the treatment of trichomoniasis: "**The July 2010 issue of Treatment Guidelines from The Medical Letter®** recommends tinidazole as a 'drug of choice' for BV and trichomoniasis" (bolded emphasis original; underlined emphasis added). The sales sheet is misleading because it fails to

[7] Bakshi JS, Ghiara JM, Nanivadekar AS. How does tinidazole compare with metronidazole? A summary report of Indian trials in amoebiasis and giardiasis. Drugs. 1978;15 (Suppl 1):33-42.
[8] "Tindamax Prescribing Information."

communicate material information from Tindamax's full FDA-approved indication for the treatment of trichomoniasis, including important information regarding diagnostic procedures and the need to treat sexual partners simultaneously. Specifically, according to the INDICATIONS AND USAGE section of the PI:

> Tinidazole is indicated for the treatment of trichomoniasis caused by *Trichomonas vaginalis*. The organism should be identified by appropriate diagnostic procedures. Because trichomoniasis is a sexually transmitted disease with potentially serious sequelae, partners of infected patients should be treated simultaneously in order to prevent re-infection.

We acknowledge the statements, "Please see attached Full Prescribing Information, including Boxed Warning" and "**Its use should be reserved for the conditions described in INDICATIONS AND USAGE**"; however, these statements do not mitigate the misleading omission of important material facts (emphasis original).

Unsubstantiated Claim

The sales sheet presents the following claim (bolded emphasis original): "**Patient-friendly convenience**." This claim is misleading because it implies that, overall, treatment with Tindamax offers "patient-friendly convenience," when this is not supported by substantial evidence. Overall patient convenience encompasses a variety of factors such as dosage and administration, all aspects of efficacy, adverse reactions, and cost. We are not aware of any evidence to support the implication that the effects of the drug, combined with its risks, translate into an overall convenient treatment for patients. Additionally, Tindamax requires multiple tablets to be taken with food and patients must abstain from alcoholic beverages while taking tinidazole and for three days afterwards. Therefore, in the absence of substantial evidence, claims suggesting that Tindamax offers overall convenience to patients are misleading.

Conclusion and Requested Action

For the reasons discussed above, the sales sheet misbrands Tindamax within the meaning of the FD&C Act, and makes its distribution violative. 21 U.S.C. 352(a); 321(n); 331(a); 21 CFR 1.21(a). *Cf*. 21 CFR 202.1(e)(5)(i), (iii); (e)(6)(i), (ii); (e)(7)(i). The sales sheet also provides evidence that Tindamax 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 Tindamax misbranded or otherwise makes its distribution violative. *See* 21 U.S.C. 355(a); 352(f); 331(a), (d); 21 CFR 201.5; 201.100; 201.115.

OPDP requests that Mission immediately cease violating the FD&C Act, as discussed above. Please submit a written response to this letter on or before February 6, 2014, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Tindamax that contain presentations such as those described above, and explaining your plan for discontinuing use of such materials.

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 or by facsimile at (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 #45 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 Untitled 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 Tindamax comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Christine Corser, Pharm.D., RAC
Regulatory Review Officer
Office of Prescription Drug Promotion

{See appended electronic signature page}

Amy Toscano, Pharm.D., RAC, CPA
Team Leader
Office of Prescription Drug Promotion

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

/s/

CHRISTINE G CORSER
01/23/2014

AMY TOSCANO
01/23/2014