DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Jean-Paul Clozel, M.D.
Chief Executive Officer
Actelion Pharmaceuticals US, Inc.
5000 Shoreline Court, Suite 200
South San Francisco, CA 94080

RE: NDA #21-290
Tracleer® (bosentan) Tablets
MACMIS #16968

WARNING LETTER

Dear Dr. Clozel:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed your Sildenafil Flash Card (07 341 01 00 0807) (flash card) for Tracleer® (bosentan) tablets (Tracleer) submitted by Actelion Pharmaceuticals US, Inc. (Actelion) under cover of Form FDA-2253. The flash card omits material information, thereby presenting an unsubstantiated superiority claim for Tracleer, and omits some of the most serious and important risk information associated with the use of Tracleer. Thus, the flash card misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) and 321(n). *Cf*. 21 CFR 202.1(e)(3)(i); (e)(6)(i) & (e)(6)(ii). These violations are concerning from a public health perspective because they suggest that Tracleer is safer and more effective than has been demonstrated.

Background

Tracleer is approved under the Subpart H regulations, 21 CFR 314.520, with a risk management program including restrictions on distribution and a boxed warning due to the potential for the drug to cause liver injury and major birth defects. In addition, Tracleer was deemed to require a risk evaluation and mitigation strategy (REMS) based on the elements to assure safe use in its risk management program.[1]

The INDICATIONS and USAGE section of the approved product labeling (PI)[2] states:

> Tracleer is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with WHO Class III or IV symptoms, to improve exercise ability and decrease the rate of clinical worsening.

[1] See 73 Fed. Reg. 16,313, 16,314 (March 27, 2008).
[2] The PI that was disseminated with the flash card and referred to within this letter was dated February 15, 2007.

In addition to the boxed warning, the co-administration of cyclosporine A and Tracleer is contraindicated due to observed, markedly increased plasma concentrations of bosentan. The co-administration of glyburide and Tracleer is contraindicated due to an observed increased risk of liver enzyme elevations. The PI also contains warnings and precautions regarding pre-existing liver impairment, hematologic changes, fluid retention, pulmonary veno-occlusive disease, other drug interactions, and use in special populations. The most common adverse events reported in clinical trials in patients treated with bosentan, and that were more common on bosentan rather than placebo, were headache (22% vs. 20%), nasopharyngitis (11% vs. 8%), flushing (9% vs. 5%), hepatic function abnormal (8% vs. 3%), edema, lower limb (8% vs. 5%), hypotension (7% vs. 4%), palpitations (5% vs. 1%), dyspepsia (4% vs. 0%), edema (4% vs. 3%), fatigue (4% vs. 1%), and pruritus (4% vs. 0%).

Selected Prior Communications with DDMAC

DDMAC has expressed the following concerns to Actelion previously in writing:

On October 30, 2002, DDMAC sent Actelion an Untitled letter, citing Actelion for false or misleading oral representations made about the use of Tracleer in congestive heart failure (CHF), and the failure to disclose any information regarding the risks associated with Tracleer therapy.

On July 20, 2005, DDMAC sent Actelion a Warning Letter, citing Actelion for its false or misleading product page on the Actelion website (www.actelion.com) for Tracleer. The product page omitted material facts regarding important risk information associated with the use of Tracleer, overstated the efficacy of Tracleer, made unsubstantiated superiority claims, and contained claims that broadened the indication for Tracleer.

On January 19, 2007, a telephone conference was held between Actelion and members of DDMAC and the Office of Medical Policy (OMP) to attempt to resolve areas of disagreement regarding previous advisory comments. In particular, the omission of the product's contraindications to glyburide and cyclosporine A was discussed. In response to Actelion's concerns regarding the clinical relevance of the contraindications included in the PI, FDA made it clear to Actelion that it considered the disclosure of major risk information, including these contraindications, clinically meaningful. A written record of this discussion was provided to Actelion on February 5, 2007.

On February 14, 2007, Actelion responded in writing to the February 5, 2007, record of the telephone conference. With regard to the contraindications related to glyburide and cyclosporine A, Actelion informed FDA that ". . . [it] does not intend to implement this suggestion . . . [but] will include a discussion of contraindications in longer promotional labeling pieces, like the sales aid."

On March 20, 2007, DDMAC provided a response to Actelion's February 14, 2007, correspondence. DDMAC reiterated its position that based on the observed risks described in the CONTRAINDICATIONS section of the PI with regard to cyclosporine A and glyburide, the omission of this important risk information is misleading. DDMAC again provided advisory comments recommending incorporating this important risk information into Actelion's promotional materials.

On September 29, 2006 and August 13, 2007, DDMAC provided advisory comments regarding Actelion's Sildenafil Head to Head Flash Card. In both letters, DDMAC commented on the omission of important risk information related to contraindications associated with the use of Tracleer with cyclosporine A and glyburide, and unsubstantiated superiority claims regarding the effectiveness of Tracleer compared to the lack of efficacy of sildenafil. DDMAC further noted that a PI-to-PI comparison of Tracleer and sildenafil does not represent substantial evidence or substantial clinical experience to support the comparative claims.

Omission of Material Information/Unsubstantiated Superiority Presentation

Promotional materials are misleading if they fail to reveal material facts with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The flash card presents a table of various claims regarding the superiority of Tracleer therapy versus sildenafil therapy. Specifically, the table presents the following questions:

- "Indicated to reduce the risk of clinical worsening?";
- "Over 2 years of follow-up data in PAH clinical trials?";
- "Prescribed to over 40,000 PAH patients, and over 5 years of clinical PAH experience?"; and
- "Blocks the devastating effects of endothelin?*"

The answers presented in response to each of these questions are "YES" for Tracleer and "NO" for sildenafil (emphasis in original), and the table is presented in conjunction with the claim, "**When initiating PAH therapy**. . . **Don't take NO for an answer**" (emphasis in original). The overall presentation suggests that Tracleer is a better treatment option than sildenafil when physicians are initiating PAH therapy for a patient. Although the questions and answers in the flash card presentation may be true, without a comparison of the risks associated with the products, the flash card misleadingly suggests that Tracleer is a better treatment option for PAH than sildenafil. It is misleading to imply that solely based on the four questions and answers comparing Tracleer with sildenafil, Tracleer is a superior treatment option for practitioners to prescribe when initiating PAH therapy. Specifically, the flash card omits material information about other attributes of Tracleer therapy, including serious risks, that are highly relevant to any decision about whether to prescribe Tracleer or sildenafil. Tracleer is associated with serious and significant risks that are not a concern when using sildenafil in PAH patients. For example, Tracleer is approved under a risk management program including restricted distribution (the TRACLEER® Access Program), and is associated with a boxed warning due to the risks of potential liver injury and major birth defects. However, sildenafil has none of these restrictions or warnings. In addition, Tracleer was deemed to have a REMS, a strategy necessary to ensure that the benefits of the drug outweigh the risks of the product, whereas sildenafil has no such designation or requirement. This comparative presentation in the flash card misleadingly omits any mention of these attributes of the drugs, and therefore suggests that Tracleer is a superior therapy.

Moreover, FDA is not aware of any substantial evidence or substantial clinical experience that Tracleer is safer, more effective, or otherwise superior to sildenafil for this patient population. The references cited in support of the above claims, including the PIs for

Tracleer and Revatio (sildenafil citrate), do not provide substantial evidence to support the implication that Tracleer is a superior treatment option to sildenafil therapy.

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are 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. Although the flash card presents numerous efficacy claims, it fails to communicate some of the most serious and important risks associated with the use of Tracleer. As stated above, the use of Tracleer is contraindicated in patients treated concomittantly with cyclosporine A due to markedly increased plasma concentrations of bosentan. The use of Tracleer is also contraindicated in patients treated concomittantly with glyburide due to an increased risk of liver enzyme elevations. The flash card fails to include either contraindication, despite the seriousness of these risks. The fact that the flash card contains the statement, "*Please see accompanying full prescribing information.*" (emphasis in original) on page two does not mitigate these misleading omissions.

Conclusion and Requested Action

For the reasons discussed above, the flash card misbrands Tracleer in violation of the Act, 21 U.S.C. 352(a) and 321(n). *Cf*. 21 CFR 202.1(e)(3)(i); (e)(6)(i) & (e)(6)(ii).

DDMAC requests that Actelion immediately cease the dissemination of violative promotional materials for Tracleer such as those described above. Please submit a written response to this letter on or before December 9, 2008, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) in use for Tracleer as of the date of this letter, identifying which of these materials contain violations such as those described above, and explaining your plan for discontinuing use of such violative 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 corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, or facsimile at (301) 847-8444. Please refer to MACMIS ID # 16968 and NDA # 21-290 in all future correspondence relating to this matter. DDMAC 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 Tracleer 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 Abrams, R.Ph., 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

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