DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED VIA FACSIMILE

Tom Lategan, Ph.D.
Actelion Pharmaceuticals US, Inc.
56 Huckleberry Lane
North Andover, MA 01845

RE: NDA # 21-290
Tracleer (bosentan) Tablets
MACMIS ID # 11014

Dear Dr. Lategan:

This letter notifies Actelion Pharmaceuticals US, Inc. (Actelion) that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified promotional activities for Tracleer (bosentan) that are in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Specifically, a territory manager from Actelion made false or misleading oral representations about Tracleer's use in congestive heart failure (CHF) to a staff member of a congestive heart failure service at a hospital in [redacted] in May 2002. Furthermore, this territory manager failed to discuss any information regarding the risks associated with Tracleer therapy. Given the elaborate risk management system developed to deal with the considerable toxic potential of Tracleer, this behavior is particularly troubling. Our specific objections follow:

Promotion of Unapproved Use

Promotional activities are misleading if they suggest that a drug is useful in a broader range of patients or conditions than has been demonstrated by substantial evidence or substantial clinical experience. 21 CFR § 202.1(e)(6). The *Indications and Usage* section of the approved product labeling (PI) states, "Tracleer is indicated for the treatment of pulmonary arterial hypertension in patients with WHO [World Health Organization] Class III or IV symptoms, to improve exercise ability and decrease the rate of clinical worsening."

Your territory manager entered a hospital office marked with a sign that reads "Congestive Heart Failure Service." The representative then made the following false or misleading statements to a staff member:

- Tracleer may be useful for the treatment of CHF

- Studies conducted on the use of Tracleer for the treatment of CHF were neither positive nor negative so the drug may have a use in these patients

These statements suggest that Tracleer may be useful for the treatment of CHF. As you know, Tracleer is not indicated for CHF and currently available data from controlled trials do not support the use of Tracleer for this indication. The results of the ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure) trial, sponsored by Actelion and Genentech, were recently presented at the American College of Cardiology 51st Annual Scientific Session in Atlanta, Georgia, in March 2002. The trial showed no favorable effect on the primary endpoint of all-cause mortality and hospitalization for CHF. Moreover, the use of Tracleer for CHF was associated with significant risks. Specifically, patients taking Tracleer in ENABLE experienced short-term worsening of CHF and immediate and sustained fluid retention. The findings also suggest that early fluid retention had an adverse prognostic effect. The ENABLE trial also showed an excess of abnormal liver function tests in the Tracleer-treated group. The promotion of Tracleer for the unapproved use in the treatment of CHF in the face of studies that show risk, and not benefit, is misleading and potentially dangerous to patients.

In addition, your territory manager failed to present any information on the risks associated with the use of Tracleer. Specifically, with respect to the serious and significant risks associated with this drug the PI includes boxed warnings that state:

> ***Use of Tracleer requires attention to two significant concerns: 1) potential for serious liver injury, and 2) potential damage to a fetus.***
>
> ***WARNING: Potential liver injury***
>
> ***Tracleer causes at least 3-fold (upper limit of normal;ULN) elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious liver injury, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly.***
>
> ***CONTRAINDICATION: Pregnancy***
>
> ***Tracleer (bosentan) is very likely to produce major birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals. Therefore, pregnancy must be excluded before the start of treatment with Tracleer and prevented thereafter by the use of a reliable method of contraception.***
>
> ***Because of potential liver injury and in an effort to make the chance of fetal exposure to Tracleer (bosentan) as small as possible, Tracleer may be prescribed only through the Tracleer Access Program by calling 1 866 228 3546.***

The omission of risk information constitutes a misrepresentation concerning the relative safety of Tracleer, thus providing additional evidence of intended use inconsistent with

the product's approved labeling. We are very concerned about this failure to discuss the risks associated with Tracleer, a drug approved under the subpart H regulations with restrictions on distribution because of the potentially serious risks associated with the product. Your omission of this important risk information raises serious public health and safety concerns.

To address these objections, we recommend that Actelion do the following:

1. Immediately cease making such violative statements and cease the distribution or use of any promotional materials for Tracleer that contain the same or similar issues.
2. Respond to this letter within ten days. Your response should include a statement of your intent to comply with the above, a list of all promotional materials with the same or similar issues, and your methods for discontinuing these promotional materials.

If you have any further questions, please direct them to me by facsimile at 301-594-6771 or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind you that only written communications are considered official.

In all future correspondence regarding this particular matter please refer to MACMIS ID #11014 in addition to the NDA number.

Sincerely,

{See appended electronic signature page}

Andrew S.T. Haffer, Pharm.D.
Regulatory Review Officer
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/

Andrew Haffer
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