DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Shal Jacobovitz
President
Actelion Pharmaceuticals US, Inc.
5000 Shoreline Court, Suite 200
South San Francisco, CA 94080

Re: NDA 21-290
Tracleer® (bosentan) Tablets
MACMIS 13061

WARNING LETTER

Dear Mr. Jacobovitz:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a product page on the Actelion website (www.actelion.com) for Tracleer® (bosentan) Tablets. The Tracleer product page is found through the "Products" link on the Actelion homepage. The Tracleer product page is false or misleading because it omits material facts regarding important risk information associated with the use of Tracleer, overstates the efficacy of Tracleer, makes unsubstantiated superiority claims, and contains claims that broaden the indication for Tracleer. Therefore, the Tracleer product page misbrands Tracleer in violation of sections 502(a) and (n) and 201(n) of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(a) & (n); 321(n), and FDA implementing regulations. 21 CFR 202.1(e)(5)(i). In addition, the Tracleer product page was not submitted to FDA at least 30 days prior to the initial dissemination of the promotional material as required by 21 CFR 314.550. Given the risks associated with the use of Tracleer, these violations present serious public health and safety concerns.

Background

Tracleer is an endothelin receptor antagonist approved under the Subpart H regulations, 21 CFR 314.520, with an elaborate 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. According to the INDICATIONS AND USAGE section of Tracleer's approved product labeling (PI), "TRACLEER is indicated for the treatment of pulmonary arterial hypertension [PAH] in patients with WHO Class III or IV symptoms, to improve exercise ability and decrease the rate of clinical worsening (see **Clinical Studies**)."

The PI for Tracleer includes a boxed warning that states (in pertinent part):

> **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 (see WARNINGS: Potential Liver Injury and DOSAGE AND ADMINISTRATION).**
>
> **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 (see CONTRAINDICATIONS). Therefore, pregnancy must be excluded before the start of treatment with TRACLEER and prevented thereafter by the use of a reliable method of contraception…. Monthly pregnancy tests should be obtained.**
>
> **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. Adverse events can also be reported directly via this number.**

The PI also contains several contraindications, warnings, precautions, and adverse events. The PI states (in pertinent part):

> **CONTRAINDICATIONS**
>
> **Pregnancy Category X:** TRACLEER is expected to cause fetal harm if administered to pregnant women.
>
> **Cyclosporine A:** Co-administration of cyclosporine A and bosentan resulted in markedly increased plasma concentrations of bosentan. Therefore, concomitant use of TRACLEER and cyclosporine A is contraindicated.
>
> **Glyburide:** An increased risk of liver enzyme elevations was observed in patients receiving glyburide concomitantly with bosentan. Therefore, co-administration of glyburide and TRACLEER is contraindicated.

PRECAUTIONS

Hematologic Changes

Treatment with TRACLEER caused a dose-related decrease in hemoglobin and hematocrit. Hemoglobin levels should be monitored after 1 and 3 months of treatment and then every 3 months.

In pertinent part, the Adverse Events section of the PI for Tracleer indicates that the adverse events occurring more frequently in patients treated with Tracleer than control group patients were headache (22% vs 20%), nasopharyngitis (11% vs 8%), flushing (9% vs 5%), and abnormal liver function (8% vs 3%).

Additionally, the PI's DOSAGE AND ADMINISTRATION General section contains important information concerning the dosage adjustment and monitoring of patients on Tracleer who develop aminotransferase abnormalities.

The CLINICAL PHARMACOLOGY Clinical Studies section of Tracleer's PI contains information regarding Tracleer's clinical trials. In pertinent part, this section indicates:

BREATHE-1 (N=213) and Study 351 (N=32) were both randomized, double-blind, multi-center, placebo-controlled trials studying patients with severe (WHO functional Class III-IV) pulmonary arterial hypertension (PAH) who received Tracleer or placebo given at a dose of 62.5 mg b.i.d. for 4 weeks and then at 125 mg b.i.d. or 250 mg b.i.d. for either 12 (BREATHE-1) or 8 (Study 351) additional weeks. The primary study endpoint was 6-minute walk distance. At 3 and 4 months, patients were able to walk 35 and 76 meters farther than patients receiving placebo in 6 minutes in the BREATHE-1 and Study 351, respectively. Time from randomization to clinical worsening was measured at week 16 of the BREATHE-1 trial and again in a smaller subset of patients at week 28 (N=35 in the bosentan group and 13 in the placebo group). Clinical worsening was assessed as the sum of death, hospitalizations for PAH, discontinuation of therapy because of PAH, and need for epoprostenol. A significant reduction in the rate of clinical worsening was demonstrated at weeks 16 and 28.

In a two year follow-up of the 235 patients participating in the BREATHE-1 and Study 351 trials, 93% and 84% of the patients were still alive at 1 and 2 years, respectively. According to the Long-term Treatment section of the PI, "These estimates may be influenced by the presence of epoprostenol [Flolan] treatment, which was administered to 43/235 patients." The PI further states that "Without a control group, these data must be interpreted cautiously and **cannot be interpreted as an improvement in survival**" (emphasis added).

Prior Communications with DDMAC

DDMAC has expressed the following concerns to you in writing previously. On October 30, 2002, DDMAC sent Actelion an untitled letter regarding false or misleading oral representations made about the use of Tracleer in congestive heart failure (CHF), as well as your failure to disclose any information regarding the risks associated with Tracleer therapy. In that letter, we requested that you discontinue promotional materials containing the same or similar representations. In a letter dated

November 11, 2002, Actelion agreed to remind the sales force not to promote Tracleer for CHF and to "not omit the presentation of risk information, such as the boxed warning information referenced" in the October 30, 2002, DDMAC letter.

On January 27, 2003, a meeting was held between Actelion, members of DDMAC, and the Office of Medical Policy (OMP) to resolve areas of disagreement regarding previous advisory comments DDMAC had provided concerning claims and representations made in two case studies and a sales aid. According to Actelion, the meeting did not resolve what Actelion considered the most important issues and, on May 27, 2003, Actelion requested a formal dispute resolution by Janet Woodcock, M.D.

On September 30, 2003, a meeting was held between Actelion, members of DDMAC, and OMP. This meeting was held in response to Actelion's request for formal dispute resolution at the Division level after the request for an appeal above the Division level was denied per a letter from the FDA dated June 13, 2003. The appeal for resolution concerned the use of claims and representations about Tracleer's indication and usage, risks, and effectiveness in two case studies, a sales aid, and two promotional flyers. In pertinent part, agreement was reached on the following issues:

- Indication and Usage: Tracleer is not indicated for all PAH patients. Actelion agreed to clearly present that Tracleer is only indicated for the treatment of PAH in "WHO Class III or IV" patients.

- Presentation of Risk Information: Actelion agreed to include in future materials, in addition to other risk information, the statement, "High potential for major birth defects: Pregnancy must be excluded and prevented by two forms of birth control; monthly pregnancy tests should be obtained."

DDMAC provided advisory comments for the Tracleer website (www.tracleer.com) on November 24, 2004. The Tracleer product page on Actelion's website is not the same as the Tracleer website.

Omission of Material Facts

The Tracleer product page makes many efficacy claims, including:

- "Actelion's first product Tracleer® (bosentan), a dual endothelin receptor antagonist (ERA), is an oral treatment for pulmonary arterial hypertension (PAH), a chronic, life-threatening disorder which is characterized by abnormally high blood pressure in the arteries between the heart and lungs."

- "With Tracleer®, they [physicians] can target the underlying mechanism of the disease, reduce symptoms, delay the time to clinical worsening and significantly increase the patient's quality of life."

However, the Tracleer product page and the five links (Healthcare Professionals, Patient Information, Endothelin System, Product Availability, Links of Interest) found on the page fail to include any information on the risks associated with the use of Tracleer. Your omission of this important risk information raises serious public health and safety concerns.

Overstatement of Efficacy

The Tracleer product page includes the following paragraph:

> "Before Tracleer®, there was not much incentive for doctors to diagnose PAH, as it was invariably fatal and treatment was a huge burden on the patient. The only product available for PAH patients had to be administered intravenously through a catheter inserted directly into the heart. Tracleer® represents a paradigm shift in treatment. Now, physicians can offer more than hope. With Tracleer®, they [physicians] can target the underlying mechanism of the disease, reduce symptoms, delay the time to clinical worsening and significantly increase the patient's quality of life."

This presentation misleadingly overstates the efficacy of Tracleer. Specifically, the statement that PAH was "invariably fatal" before Tracleer implies that a survival benefit has been shown for PAH patients who receive Tracleer therapy. Furthermore, the phrase "Now, physicians can offer more than hope," creates the suggestion that Tracleer has been shown to improve survival. FDA is not aware of substantial evidence or substantial clinical experience demonstrating a survival benefit for Tracleer. The Long-term Treatment section of Tracleer's PI points out that survival was measured, but adds that "Without a control group, these data must be interpreted cautiously and cannot be interpreted as an improvement in survival."

In addition, the claim that Tracleer "significantly increase[s] the patient's quality of life" is not substantiated by evidence. The claim that Tracleer "significantly increase[s] the patient's quality of life" suggests to physicians and others in the medical profession that evidence exists demonstrating a treatment benefit on important domains of health related quality of life measures, such as might be shown through the use of validated Patient Reported Outcome Instruments. While Tracleer improves the number of meters patients can walk and decreases the rate of clinical worsening in PAH patients with WHO Class III or IV symptoms, benefits that would undoubtedly be recognized by the patient, we are not aware of any evidence that these effects of the drug, combined with the drug's side effects, translate into a significant improvement on patients' quality of life.

Unsubstantiated Superiority Claim

In addition to overstating the efficacy of Tracleer, the paragraph excerpted above misleadingly suggests that Tracleer is superior to an existing therapy when this has not been demonstrated by substantial evidence or substantial clinical experience. Specifically, the claim "The only product available for PAH patients [before Tracleer] had to be administered intravenously through a catheter inserted directly into the heart" refers to the drug product Flolan (epoprostenol), which is administered by continuous intravenous infusion via a central venous catheter using an ambulatory pump. This claim, in conjunction with the claims "Before Tracleer®, there was not much incentive for doctors to diagnose PAH" and "Tracleer® represents a paradigm shift in treatment," which now allows physicians to "offer more than hope," suggests that Tracleer is superior to Flolan. In fact, the CLINICAL TRIALS IN PULMONARY HYPERTENSION section of the PI for Flolan indicates that Flolan showed improved survival in NYHA functional Class III and Class IV primary pulmonary hypertension patients. In contrast, a survival benefit of Tracleer has not been demonstrated for any population. DDMAC is not aware of any studies comparing the effectiveness of Tracleer to Flolan for

any endpoint. DDMAC is particularly concerned about the unsubstantiated superiority claim because Flolan has demonstrated an improvement in survival while Tracleer has not.

Additionally, the claim that "the only product available for PAH patients had to be administered intravenously through a catheter inserted directly into the heart" is false and is inappropriately alarming. Flolan (epoprostenol), the product referenced in the claim, is administered by continuous intravenous infusion via a central venous catheter inserted into a large vein above the heart.

The comparison with Flolan is also misleading in another respect. While it is appropriate to point out the benefit of the oral route of administration compared to administration via a central venous line, Tracleer is associated with other serious risks. Unlike Flolan, Tracleer is hepatotoxic, requiring periodic monitoring, and teratogenic, requiring stringent attention to contraception.

Broadening of Indication

The Tracleer product page also contains the claim "Actelion's first product Tracleer® (bosentan), a dual endothelin receptor antagonist (ERA), is an oral treatment for pulmonary arterial hypertension (PAH), a chronic, life-threatening disorder which is characterized by abnormally high blood pressure in the arteries between the heart and lungs." As FDA has indicated in previous communications with Actelion, this claim misleadingly broadens the indication because it fails to present the limitation to the product's indication, i.e., that Tracleer is only indicated for patients with PAH WHO Class III or IV symptoms.

Failure to Submit Promotional Materials

The Tracleer product page was not submitted to FDA 30 days prior to its initial dissemination, as required by the Subpart H regulations regarding promotional materials, 21 CFR 314.550.

Conclusion and Requested Action

Your website fails to reveal material facts regarding important risk information associated with the use of Tracleer, suggests that Tracleer is more effective than has been demonstrated by substantial evidence or clinical experience, and makes unsubstantiated superiority claims in violation of 21 U.S.C. 352(a) & (n) and 321(n) and FDA implementing regulations. 21 CFR 202.1(e)(5)(i). In addition, the Tracleer product page was not submitted to FDA at least 30 days prior to the initial dissemination of the material as required by 21 CFR 314.550. These violations pose serious public health and safety concerns.

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 August 03, 2005, stating whether you intend to comply with this request, listing all violative promotional materials for Tracleer 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 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. 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, MD 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer to MACMIS #13061 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 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 W. Abrams, R.Ph., M.B.A.
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/

Melissa Moncavage
7/20/05 03:59:57 PM
Signed for Thomas W. Abrams

Products

Tracleer®

Healthcare Professionals
Patient Information
Endothelin System
Product Availability
Links of Interest

Zavesca®

Tracleer®

Actelion's first product Tracleer® (bosentan), a dual endothelin receptor antagonist (ERA), is an oral treatment for pulmonary arterial hypertension (PAH), a chronic, life-threatening disorder which is characterized by abnormally high blood pressure in the arteries between the heart and lungs. Tracleer® works by blocking the detrimental affects of endothelin, a substance secreted by the endothelium, a single layer of cells covering the inner surface of blood vessels.

Approximately 100,000 people in Europe and the United States are afflicted with either idiopathic pulmonary arterial hypertension (IPAH) or forms of the disease secondary to other conditions. Because the most common symptom o pulmonary arterial hypertension, dyspnea (breathlessness), can be caused by number of diseases, PAH is often misdiagnosed. In fact, the average time for correct diagnosis is two to three years, which leaves the patient with precious few years to live once the medical findings have been confirmed.

Before Tracleer®, there was not much incentive for doctors to diagnose PAH, a it was invariably fatal and treatment was a huge burden on the patient. The only product available for PAH patients had to be administered intravenously through a catheter inserted directly into the heart. Tracleer® represents a paradigm shift in treatment. Now, physicians can offer more than hope. With Tracleer®, they can target the underlying mechanism of the disease, reduce symptoms, delay the time to clinical worsening and significantly increase the patient's quality of life.

Actelion markets Tracleer® through its own subsidiaries in key markets worldwide, including the United States (based in South San Francisco), the European Union as well as Canada, Israel, Australia and Switzerland.