



NDA 21-290/S-014

Actelion Pharmaceuticals, Ltd.  
Attention: Brian D. Schlag, MA, MS  
1820 Chapel Avenue West, Suite 300  
Cherry Hill, NJ 08002

## SUPPLEMENT APPROVAL

Dear Mr. Schlag:

We refer to your supplemental New Drug Application (S-014) submitted September 5, 2008, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tracleer (bosentan) 62.5 and 125 mg Tablets.

We also acknowledge receipt of your submission dated September 24, 2008.

Your reasons for submitting S-014 were two-fold: 1) To provide the final study report for study AC-052-402 to satisfy the postmarketing commitment to investigate the potential testicular toxicity of Tracleer in humans, and 2) To provide a prior approval labeling supplement to incorporate the results from study AC-052-402 into the package insert and Medication Guide for Tracleer.

1) With regard your postmarketing commitment (#1):

1. Investigation of the potential testicular toxicity of Tracleer in humans.

We sent you a letter on December 22, 2008 that acknowledged you had fulfilled this postmarketing commitment.

2) With regard to your prior approval labeling supplement:

This supplemental new drug application provides for revisions to the Full Prescribing Information and the Medication Guide as agreed to per email correspondence dated February 2, 2009:

➤ To add the following text to the **WARNINGS** section of the package insert:

*Decreased Sperm Counts*

An open-label, single arm, multicenter, safety study evaluated the effect on testicular function of **TRACLEER**® 62.5 mg b.i.d. for 4 weeks, followed by 125 mg b.i.d for 5 months. Twenty-five male patients with WHO functional class III and

IV PAH and normal baseline sperm count were enrolled. Twenty-three completed the study and 2 discontinued due to adverse events not related to testicular function. There was a decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment with **TRACLEER®**. Sperm count remained within the normal range in all 22 patients with data after 6 months and no changes in sperm morphology, sperm motility, or hormone levels were observed. One patient developed marked oligospermia at 3 months and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. **TRACLEER®** was discontinued and after two months the sperm count had returned to baseline levels. Based on these findings and preclinical data from endothelin receptor antagonists, it cannot be excluded that endothelin receptor antagonists such as **TRACLEER®** have an adverse effect on spermatogenesis.

- To change the following text in the **What are the possible side effects of Tracleer** section of the Medication Guide:

FROM

**Low sperm count.** Drugs like Tracleer lower sperm count in animals. If this happens in men taking Tracleer, they may lose the ability to father children.

TO

**Sperm Count Reduction.** Reduced sperm counts have been observed in some men on Tracleer, which might impair ability to father a child. Tell your doctor if remaining fertile is important to you.

We refer to previous labeling agreements reached in June 2008 regarding the following labeling changes:

- To add “Jaundice, Anemia requiring transfusion” to the **ADVERSE REACTIONS/Post-Marketing Experience** section of the package insert.
- To add the following text to the **OVERDOSAGE** section of the package insert:

In the postmarketing period, there was one reported overdose of 10,000 mg of bosentan taken by an adolescent male patient. He had symptoms of nausea, vomiting, hypotension, dizziness, sweating, and blurred vision. He recovered within 24 hours with blood pressure support.

Bosentan is unlikely to be effectively removed by dialysis due to the high molecular weight and extensive plasma protein binding.

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format as described at

<http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, “**SPL for approved NDA 21-290/S-014.**”

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH  
Food and Drug Administration  
Suite 12B05  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Dan Brum, PharmD, MBA, RAC, Regulatory Project Manager, at (301) 796-0578.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal  
Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure: Agreed-upon labeling text

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Norman Stockbridge  
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