



NDA 21-290/S-006 and S-007

Actelion Ltd.
Attention: Mr. Tom Lategan, Ph.D.
5000 Shoreline Court, Suite 200
South San Francisco, CA 94080

Dear Dr. Lategan:

Please refer to your supplemental new drug applications (sNDAs) dated March 11, 2005 (S-006) and May 9, 2005 (S-007), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tracleer (bosentan) 62.5 and 125 mg Tablets.

We acknowledge receipt of your submissions dated May 26, August 12, September 6, October 21, and November 14, 2005.

These supplemental new drug applications provide for revisions to the Black Box Warning, Clinical Pharmacology, Indications and Usage, Warnings, Precautions, and Adverse Reactions sections of the approved package insert and the Medication Guide.

We completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and Medication Guide). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidances specify that labeling is to be submitted in *pdf* format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper.

We remind you of your postmarketing study commitments in your submission dated November 14, 2005. These commitments are listed below.

1. Letter to Tracleer prescribers: Within 21 days of reaching agreement on the text of the letter, and after Agency approval of the revised product information, the letter plus revised product information will be mailed to all US Tracleer prescribers.

2. Planned survey of physician practice: Your proposed plan for a survey will be submitted to the Division by January 15, 2006.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Commitment Protocol," "Postmarketing Study Commitment Final Report," or "Postmarketing Study Commitment Correspondence."

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 Ms. Melissa Robb, Regulatory Health Project Manager, (301) 796-1138.

Sincerely,

{See appended electronic signature page}

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

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

Norman Stockbridge
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