DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-290/S-004

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

Dear Dr. Lategan:

Please refer to your supplemental new drug application dated August 9, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tracleer (bosentan) 62.5 and 125 mg Tablets.

We also refer to your submission dated August 19, 2004.

This supplemental new drug application proposes the following changes to the package insert:

1. In the **CONTRAINDICATION: Pregnancy** section of the boxed warning, the third sentence of the first paragraph of the has been changed from:

   Hormonal contraceptives, including oral, injectable, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving TRACLEER® (see Precautions: Drug Interactions).

   To:

   Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving TRACLEER® (see Precautions: Drug Interactions).

2. In the **CONTRAINDICATIONS/Pregnancy Category X** section, the second sentence of the second paragraph of the has been changed from:

   Hormonal contraceptives, including oral, injectable, and implantable contraceptives may not be reliable in the presence of TRACLEER® and should not be used as the sole contraceptive method in patients receiving TRACLEER® (see **Drug Interactions**: Hormonal Contraceptives, Including Oral, Injectable, and Implantable Contraceptives).

   To:

It has been demonstrated that hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives may not be reliable in the presence of TRACLEER® and should not be used as the sole contraceptive method in patients receiving TRACLEER® (see **Drug Interactions**: Hormonal Contraceptives, Including Oral, Injectable, Transdermal and Implantable Contraceptives).

3. The title of the **PRECAUTIONS/Drug Interactions/ Hormonal Contraceptives, Including Oral, Injectable, and Implantable Contraceptives** subsection has been changed to **PRECAUTIONS/Drug Interactions/ Hormonal Contraceptives, Including Oral, Injectable, Transdermal, and Implantable Contraceptives**.

4. The **PRECAUTIONS/Drug Interactions/ Hormonal Contraceptives, Including Oral, Injectable, Transdermal, and Implantable Contraceptives** subsection has been changed from:

   Specific interaction studies have not been performed to evaluate the effect of co-administration of bosentan and hormonal contraceptives, including oral, injectable or implantable contraceptives. Since many of these drugs are metabolized by CYP3A4, there is a possibility of failure of contraception when TRACLEER® is co-administered. Women should not rely on hormonal contraception alone when taking TRACLEER®.

   To:

   An interaction study demonstrated that co-administration of bosentan and the oral hormonal contraceptive Ortho-Novum® produced average decreases of norethindrone and ethinyl estradiol levels of 14% and 31%, respectively. However decreases in exposure were as much as 56% and 66%, respectively, in individual subjects. Therefore, hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may not be reliable when TRACLEER® is co-administered. Women should practice additional methods of contraception and not rely on hormonal contraception alone when taking TRACLEER®.

5. The following subsection has been added to the **ADVERSE REACTIONS** section:

   Post-Marketing Experience: Hypersensitivity, Rash

6. The first sentence of the **DOSAGE AND ADMINISTRATION/Use in Women of Child-bearing Potential** has been changed from:

   TRACLEER® treatment should only be initiated in women of child-bearing potential following a negative pregnancy test and only in those who practice adequate contraception that does not rely solely upon hormonal contraceptives, including oral, injectable or implantable contraceptives (see **DRUG INTERACTIONS**: Hormonal contraceptives, Including Oral, Injectable and Implantable Contraceptives).

   To:

   TRACLEER® treatment should only be initiated in women of child-bearing potential following a negative pregnancy test and only in those who practice adequate contraception that does not rely solely upon hormonal contraceptives, including oral, injectable, transdermal, or

implantable contraceptives (see **DRUG INTERACTIONS**: Hormonal contraceptives, Including Oral, Injectable, Transdermal, and Implantable Contraceptives).

7. In the "**What is the most important information I should know about Tracleer?**" section of the Medication Guide attached to the package insert, the second sentence of the third paragraph has been changed from:

   Birth control pills, shots, implants, or other hormone-based birth control may not be enough when Tracleer is used.

   To:

   Birth control pills, shots, patches, implants, or other hormone-based birth control may not be enough when Tracleer is used.

8. In the "**What should I avoid while taking Tracleer?**" section of the Medication Guide attached to the package insert, the first sentence of the third point has been changed from:

   Do not use hormone-based birth control (pills, injections, implants) as your only method of birth control.

   To:

   Do not use hormone-based birth control (pills, injections, patches, implants) as your only method of birth control.

9. In the "**Other possible side effects**" section of the Medication Guide attached to the package insert, "rash" been added to the list.

We have completed our review of this application. The application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions listed below.

1. In the **CONTRAINDICATION: Pregnancy** section of the boxed warning, the following sentence should be added as the fourth sentence of the first paragraph:

   Therefore, effective contraception through additional forms of contraception must be practiced.

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted labeling (package insert dated August 9, 2004). These revisions are terms of the approval of this application.

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). These guidances specify that labeling 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.

For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-290/S-004." Approval of this submission by FDA is not required before the labeling is used.

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, HFD-410
FDA
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:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug 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 this page is the manifestation of the electronic signature.

/s/

Norman Stockbridge

11/24/04 03:09:59 PM