CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-290

Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-290

NOV 20 2001

Actelion, Ltd.
Attention: Peter Hermann, Ph.D.
Gewerbestrasse 16
Allschwill
Ch-4123 Switzerland

Dear Dr. Hermann:

Please refer to your new drug application (NDA) dated November 17, 2000, 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 September 11 and 25, October 4 and 15 and November 2, 8 and 19, 2001. Your submission of November 2, 2001 constituted a complete response to our September 17, 2001 action letter.

This new drug application provides for the use of Tracleer (bosentan) 62.5 and 125 mg Tablets for the treatment of pulmonary arterial hypertension.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to approve Tracleer (bosentan) 62.5 and 125 mg Tablets under the regulations for accelerated approval for use as recommended in the final printed labeling (package insert), Medication Guide and carton and container labels included in your November 2, 2001 submission. Accordingly, the application is approved under 21 CFR 314 subpart H (314.500 – 560). Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations (21CFR 314.520) and the specific restrictions on distribution described below.

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement. It is possible to consider different terms with the FDA at a later date.

Medication Guide

Pursuant to 21 CFR Part 208, FDA is notifying Actelion, Ltd. (hereinafter "Sponsor") that, based on information from pre-marketing studies, FDA has determined that Tracleer (bosentan) poses a serious and significant public health concern requiring distribution of the above-mentioned Medication Guide. Distribution of a Medication Guide is necessary for patients' safe and effective use of Tracleer. FDA has determined that Tracleer is a product for which patient labeling could help prevent serious adverse

effects. See 21 CFR Part 208.1(c). The Medication Guide for Tracleer must address the concerns about liver toxicity and pregnancy and the actions patients should take to avoid these serious adverse effects.

In accordance with 21 CFR 208, Actelion is responsible for ensuring the following:

- That a Medication Guide for Tracleer is available for every patient who is dispensed a prescription for Tracleer.
- That the label of each container of Tracleer includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom Tracleer is dispensed.
- That the label of each container includes a statement about how the Medication Guide is provided.

Tracleer Access Program

We remind you that your Tracleer Access Program is an important part of the postmarketing risk management for Tracleer, and must include all of the following components:

(1) Complete registration of all patients receiving Tracleer.
(2) Complete registration of practitioners who prescribe Tracleer.
(3) Distribution of Tracleer through a restricted distribution network.
(4) Distribution of the Tracleer Medication Guide to patients with each shipment of Tracleer.
(5) Initial distribution of Tracleer is to occur only after receipt by the distributor network of a written certification by the practitioner for an individual patient, stating that:

- Tracleer is being prescribed for a medically appropriate use in the treatment of Pulmonary Arterial Hypertension, as described in the Tracleer full prescribing information.
- The physician has reviewed the liver and pregnancy warnings with the patient and has committed to undertaking the appropriate monitoring of liver function tests and testing for pregnancy (if the patient is a female of child-bearing potential).

(6) An ongoing, comprehensive program to track and report to the FDA all fetal exposures to Tracleer and the outcomes of such exposures.
(7) An ongoing, comprehensive program to track and report to the FDA all adverse events related to liver injury in patients who receive Tracleer and the outcomes of those events (see below).
(8) An ongoing, comprehensive notification program that would respond to the collection of information from patients about their receipt of liver function testing and pregnancy testing in the previous month by providing (and recording) prompt feedback to the prescribing physicians about patients who are not compliant with this monitoring, or who are uncertain about their compliance with the monitoring. Such feedback must remind the physicians of the need for such ongoing monitoring.
(9) Review and assessment by the Sponsor and the FDA, at least on an annual basis, of the effectiveness of the Tracleer Access Program.

The Tracleer Access Program, as described in the attached documents, adequately addresses each of these requirements. Any changes to the program must be discussed with the FDA prior to their institution and are subject to FDA approval. We expect your continued cooperation to resolve any problems regarding the Tracleer Access Program that may be identified following Tracleer approval.

At the end of one year, and then annually, the Sponsor needs to provide the FDA with a detailed summary and analyses of the data available on all patients treated with Tracleer through the Tracleer Access Program, as a means of assessing the success of the program in minimizing patient pregnancy and liver toxicity. This summary should include the following:

- Summary demographic data on the use of Tracleer, both cumulative (from initial marketing) and during the previous year.
- Summary data on liver function monitoring and monitoring for pregnancy in patients taking Tracleer. This should include data on:
    - all feedback provided to the specialty distributors by the patients about their compliance with monthly liver function and pregnancy monitoring.
    - all feedback provided to the physicians by the specialty distributors about patient compliance with monthly liver function and pregnancy monitoring.
- Summary data on all reported clinical and laboratory adverse events related to the liver and any pregnancies.
- All materials submitted as part of the 15-day safety reports (see below).

We remind you of your specific reporting obligations regarding hepatotoxicity and pregnancies in patients who have received or are receiving Tracleer. In addition to the usual postmarketing reporting of adverse drug experiences (21 CFR 314.80), we ask that you initiate a 15-day safety report for:

- Any pregnancy.
- Any elevation in liver enzymes (aminotransferases) to > 8 times the upper limits of normal.
- Any elevations of liver enzymes (aminotransferases) accompanied by an elevation of bilirubin to ≥ 2 times upper limits of normal.
- Any clinical liver injury associated with hospitalization, liver transplant or death.

Postmarketing Studies (Phase 4 Commitments)

We remind you of your postmarketing study commitments, which are listed below.

(1) Investigation of the potential testicular toxicity of Tracleer in humans. Please submit a detailed proposal for a Phase 4 study or studies to examine the clinical effects of chronic treatment with Tracleer. Data to be collected as part of this commitment include:

- Semen analysis: total sperm count, semen volume, sperm concentration, sperm morphology and sperm motility. Analyses will need to be conducted at baseline followed by analyses through at least 6 months of drug exposure. If injury is detected, a follow-up analysis at least 3 months off drug will be important to assess reversibility.
- Assessment of the neurohormonal axis regulating male fertility: follicle stimulating hormone, inhibin, luteinizing hormone and total testosterone. Analyses will need to be conducted at baseline followed by analyses through at least 6 months of drug exposure.

(2) Investigation of potential metabolic interactions between Tracleer and hormonal contraceptives (*e.g.*, oral and implantable contraceptives). The goals of these investigations are to determine whether the use of Tracleer reduces the levels of these hormones in women through its induction of hepatic enzyme CYP 3A4 and whether the concomitant use of Tracleer decreases the effectiveness of these contraceptives in preventing ovulation. In order to characterize this effect of Tracleer adequately in humans, we ask that you submit a detailed proposal for a Phase 4 study or studies to examine the following effects of acute and chronic co-administration of Tracleer and

hormone-based contraceptives on the following parameters:

- Reproductive hormone levels in ovulating females.
- Ovulation.

Submit clinical and nonclinical protocol(s) to your IND for Tracleer and all study final reports to this NDA. In addition, under 21CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you are required to include a status summary of each commitment in your annual reports to this NDA. The status summary needs to 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 Protocol"**, **"Postmarketing Study Final Report"**, or **"Postmarketing Study Correspondence."**

Chemistry and Manufacturing Issue

A dissolution specification of not less than [redacted]% (Q) dissolved in 30 minutes in 1% sodium lauryl sulfate in water at a paddle speed of 50 rpm is recommended. Data related to this goal should be submitted to the FDA as they become available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21CFR 314.80 and 314.81.

If you have any questions, please call:

Ms. Zelda McDonald
Regulatory Health Project Manager
(301) 594-5333

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Cc:
Actelion Ltd.
Attention: Thomas W. Lategan, D.Phil.
56 Huckleberry Lane
North Andover, MA 01845

Tracleer™ Access Program (TAP)

The purpose of this document is to describe the plans for a restricted distribution network for Tracleer (Tracleer Access Program or TAP) and development of a patient database to follow patients treated with Tracleer. This plan was outlined to the FDA's Cardiovascular and Renal Drugs Advisory Committee on August 10, 2001. TAP will provide a mechanism to assist with 2 primary risk management goals for Tracleer therapy.

1. Pregnancy prevention
2. Liver enzyme monitoring and prevention of hepatic injury

Actelion is absolutely committed to a comprehensive physician and patient education campaign that will highlight these two goals.

How the TAP system works:

1. A toll free line provides physicians with initial information about Tracleer, a site to report adverse events, and provides customer service. The toll free line offers 3 choices:

   A. Press 1 - Tracleer Access Program provides initial information and contact information including fax number and patient enrollment form if needed. TAP creates and maintains a central database. TAP triages the prescription to a Specialty Distributor (SD).
   B. Press 2 – The Medical Information and Drug Safety Reporting Line. The physician or patient may ask questions, request information or report adverse events (AEs). In the event of an AE related to liver function test (LFT) elevations or pregnancy, a form is completed and faxed to Actelion for review and follow-up. This line is also the contact point with physicians if the medication is discontinued or not refilled.
   C. Press 3 – Customer Service. For all other issues.

2. Following the toll-free call, a completed Patient Enrollment Form is faxed to TAP to initiate the prescription. The form serves as the prescription, allowing a one month supply (with refills) of drug, providing patient information and including important physician certifications.

3. Each Specialty Distributor (SD) must agree to a defined set of rules to sell Tracleer. The rules include, but may not be limited to:

   A. Inserting two patient reminders in the monthly prescription:
      a. The approved Patient Medication Guide
      b. A LFT and Pregnancy testing reminder card

      Note: These will remind the patient to have LFTs checked. Females of child-bearing potential are also reminded of the importance of testing for pregnancy monthly, and preventing pregnancy using appropriate birth control methods. Patients are also reminded to contact their physician if they experience adverse events or have questions.

The SD must make a database entry verifying completion of this contact.

B. Generating a letter to the prescribing physician in which the SD indicates that the initial prescription for Tracleer has been filled (date) for the patient (name). The letter will contain the name of the SD along with a contact number for the physician to call if there is any need to alter the dosage of Tracleer. This letter will also remind the doctor to check the LFT s monthly and that female patients should not become pregnant or take Tracleer during pregnancy and should have pregnancy testing done monthly. Finally, the physician will be reminded to report any relevant AE's to the Actelion Drug Safety Reporting Line (1-866-228-3546) and/or the Food and Drug Administration (1-800-FDA-1088)

C. Calling the patient prior to the scheduled shipment of the next months medication and asking them if they are continuing on Tracleer. If they are, they should be reminded of the need for liver function tests and asked if they have had a blood draw in the last month for reasons other than checking blood thinning. If a patient is female of child-bearing potential, she should be asked if she has had a pregnancy test within the last month and be reminded that she should not become pregnant while on Tracleer.

D. If the patient has not had a liver or pregnancy test within the last month, or is unsure, then the SD will communicate this promptly to the physician and remind the physician of the need for liver and/or pregnancy monitoring. The initial call to the patient and the contact with the physician will be logged.

E. If a planned refill doesn't occur, the TAP Administrator will determine why. If the reason is medical, the physician will be contacted to determine what the medical issue is, and whether the issue is related to LFT elevation or change in pregnancy status. That information will be entered into the TAP database. Adverse events will be forwarded to the Actelion Director of Drug Safety for follow up and reporting.

4. The Patient Enrollment Form contains a statement : "I certify that I am prescribing Tracleer™ (bosentan) for this patient for a medically appropriate use in the treatment of Pulmonary Arterial Hypertension, as described in the Tracleer™ full prescribing information. I have reviewed the liver and pregnancy warnings with the patient and commit to undertaking appropriate blood testing for monitoring liver function in this patient and testing for pregnancy (if the patient is a female of child-bearing potential)." This statement is followed by a place for the physician's signature.

Tracleer™ (bosentan) Patient Enrollment

Phone 1-866-228-3546 or Fax 1-866-279-0669

PO Box 220829 Charlotte, North Carolina 28222-0829

Upon receipt of this patient enrollment form to the Tracleer Access Program (TAP), a representative will verify the patient's benefits to determine coverage, assign a specialty distributor based on benefits, and coordinate with this distributor to facilitate access to Tracleer. The specialty distributor will follow up as needed with the prescriber and will ensure appropriate distribution of the drug.

Please Select: ❑ **Newly Prescribed Patient** ❑ **Patient Currently on Tracleer** ❑ **Clinical Trial Patient**

PATIENT INFORMATION (Please print)

Name: _____ SSN#: _____ DOB: _____

Address: _____ City: _____ State: _____ Zip: _____

Phone Numbers Day: ___ - ___ - _____ Evening: ___ - ___ - _____ Sex: ❑ M ❑ F

INSURANCE INFORMATION (Include copies of insurance cards if possible)

Primary Insurance Co. Name: _____ Phone #: ___ - ___ - _____

Policy Holder Name: _____

Policy #: _____ Group #: _____

Prescription Card Name: _____ Phone #: ___ - ___ - _____

Policy #: _____ Group #: _____

Secondary Insurance Co. Name: _____ Phone #: ___ - ___ - _____

Policy Holder Name: _____ Policy #: _____ Group #: _____

I authorize The TRACLEER™ ACCESS PROGRAM and its distributors to obtain and disclose information to my insurance company, government agency or other parties, on my behalf, as necessary to obtain reimbursement approval for Tracleer™ (bosentan). My name and street address information shall not be divulged to ACTELION or any other party unless necessary to comply with laws, regulations or other requirements necessary to deal with safety, adverse event and related issues.

Patient/Guardian Signature: _____ **Date:** _____

PHYSICIAN INFORMATION

Prescriber Name & Title: _____ DEA#: _____

Name of Facility: _____ State License #: _____

Contact Name: _____ Physician

Address: _____ Specialty: _____

City: _____ Physician e-mail: _____

State: _____ Zip: _____

Phone: ___ - ___ - _____ Fax: ___ - ___ - _____

PRESCRIPTION

❑ Tracleer 62.5 mg

(66215-0101-06)

Refills # _____

❑ Tracleer 125 mg

(66215-0102-06)

Refill # _____

Instructions:

_____

_____

_____

Ship to: ❑ Physician Office ❑ Patient's home ❑ Other(specify): _____

Address (no P.O. Box): _____

City, State, Zip: _____

Ship Attn: _____

STATEMENT OF MEDICAL NECESSITY

Diagnosis: ❑ Pulmonary Arterial Hypertension (ICD _____)

Related To: ❑ Primary Pulmonary Hypertension (ICD 416.0) ❑ Scleroderma (ICD 710.1) ❑ Lupus (ICD 710.0)

❑ HIV (ICD _____) ❑ Congenital Heart (ICD _____) ❑ Other (ICD _____)

I certify that I am prescribing Tracleer™ (bosentan) for this patient for a medically appropriate use in the treatment of Pulmonary Arterial Hypertension, as described in the Tracleer™ full prescribing information. I have reviewed the liver and pregnancy warnings with the patient and commit to undertaking appropriate blood testing for monitoring liver function in this patient and testing for pregnancy (if the patient is a female of child-bearing potential).

Prescriber's Signature: **Date:**

Internal Use Only: **Date to TAP:** _____ **Patient ID:** _____

(REV16111901F1) **Assigned Distributor:** _____

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APPLICATION NUMBER
21-290

Approvable Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-290

SEP 17 2001

Actelion Ltd.
Attention: Peter Hermann, Ph.D.
Gewerbestrasse 16
Allschwill
CH-4123 Switzerland

Dear Dr. Hermann:

Please refer to your new drug application (NDA) dated November 17, 2000, 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 September 25 (presubmission), October 11, November 22, December 12, 14 and 20, 2000; January 8 and 17, March 5, 7, 14 and 23, April 23 and 27, May 9, 18 and 31, June 21 and 25, July 31, August 4, 16, 24, 28 and 30 (two) and September 4, 2001.

This new drug application proposes the use of Tracleer (bosentan) Tablets for the treatment of pulmonary arterial hypertension.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert); note that we are asking you to review significant liver injuries in your study.

Based on our assessment of the advice we received from the August 24, 2001 meeting of the Cardiovascular and Renal Drugs Advisory Committee regarding your product, Tracleer (bosentan), as well as our review of your submitted data, we request the following actions be undertaken by you. These actions relate to the post-approval risk management program for Tracleer and address our concerns related to (a) pregnancy prevention, (b) liver injury, and (c) the need for additional information about the potential effects of Tracleer on male fertility.

RISK MANAGEMENT – PREGNANCY PREVENTION

The committee asserted, and we concur, with the following two primary risk management goals with respect to efforts to prevent pregnancy in association with Tracleer usage:

(1) No one should begin Tracleer therapy if pregnant.
(2) No pregnancies should occur while on Tracleer therapy.

In order to achieve these risk management goals, we request that you submit a detailed proposal for informing the patients and the prescribing community of the severe fetal risks likely to be associated with exposure to Tracleer, as well as plans for preventing its occurrence. Examples of potential approaches to risk management include the following:

(1) An educational program for each Tracleer patient and /or parent/guardian (if the patient is under 18 years of age) that includes verifiable documented written informed consent by all female patients and/or parent/guardian (if the patient is under 18 years of age), prior to receiving Tracleer. This informed consent document would not only detail possible risks to a fetus, but should also make clear to patients and/or parent/guardian (if the patient is under 18 years of age) the indication for which Tracleer has been approved by FDA.
(2) A Medication Guide pursuant to 21CFR Part 208, probably delivered with unit-of-use packaging.
(3) A program whereby there is complete registration of female patients receiving Tracleer.
(4) A program whereby there is complete registration and certification of practitioners who prescribe Tracleer.
(5) A comprehensive program to track and report to CDER all fetal exposures to Tracleer and the outcomes of such exposures.
(6) Initiation of a comprehensive compliance program that would link dispensing of Tracleer to female patients only upon verification of adequate pregnancy testing.
(7) Development and implementation of a monitoring program that will facilitate, at a minimum on an annual basis, your and our assessment of progress towards meeting these risk management goals.

Agreement on the framework for this risk management strategy and plans for its implementation must be in place prior to the approval of Tracleer.

RISK MANAGEMENT – HEPATIC INJURY

The committee asserted, and we concur, that there is sufficient concern to justify intensive risk management with regard to the hepatic effects of Tracleer, with two primary goals:

(1) Prescribers and patients must be fully aware of the hepatic effects of Tracleer, and the need for ongoing monitoring of hepatic enzymes during therapy with Tracleer.
(2) No fatal hepatic injuries should occur as a result of Tracleer.

In order to achieve these risk management goals, we request that you submit a detailed proposal for informing the patients as well as the prescribing community of the hepatic effects of Tracleer. Examples of potential approaches to risk management include the following:

(1) Development and distribution of an enhanced prescriber educational program to educate prescribers further about the hepatic effects of Tracleer and the need for continued monitoring of both liver enzymes (*e.g.*, ALT, AST, bilirubin) and clinical signs of liver injury. Such a program could include the development of a Medication Guide pursuant to 21CFR Part 208, probably delivered with unit-of-use packaging.
(2) A program whereby there is complete registration of all patients receiving Tracleer.
(3) A program whereby there is complete registration and certification of practitioners who prescribe

Tracleer.

(4) A comprehensive program to track and report to CDER all severe liver injuries associated with the use of Tracleer and the outcomes of such events.

(5) Development and implementation of a monitoring program that will facilitate; at a minimum on an annual basis, your and our assessment of progress towards meeting these risk management goals.

Agreement on the framework for this risk management strategy and plans for its implementation must be in place prior to the approval of Tracleer.

RISK MANAGEMENT – TESTICULAR INJURY

There is evidence in the pre-clinical data submitted to NDA 21-290 of a potential toxic effect of Tracleer on the testes. In order to characterize this effect adequately in humans, we request that you submit a detailed proposal for a Phase 4 commitment to examine the clinical effects of chronic treatment with Tracleer. Data to be collected as part of this commitment include:

(1) Semen analysis: total sperm count, semen volume, sperm concentration, sperm morphology and sperm motility. Analyses will need to be conducted at baseline followed by analyses through at least 6 months of drug exposure. If injury is detected, a follow-up analysis at least 3 months off drug will be important to assess reversibility.

(2) Assessment of the neurohormonal axis regulating male fertility: follicle stimulating hormone (FSH), inhibin, luteinizing hormone and total testosterone. Analyses will need to be conducted at baseline followed by analyses through at least 6 months of drug exposure.

Agreement on the framework for these studies and plans for its implementation (including timelines for completion) must be in place prior to the approval of Tracleer.

We look forward to continued close cooperation with Actelion in achieving the risk management goals outlined for this product.

We recommend that you change the proposed dissolution medium from 1% sodium lauryl sulfate in water to( )% sodium lauryl sulfate in water with a dissolution specification of Q not less than( )% in 30 minutes.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL, ten of which individually mounted on heavy weight paper or similar material.
If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please call:

Ms. Zelda McDonald
Regulatory Health Project Manager
(301) 594-5333.

Sincerely,
{See appended electronic signature page}

Robert Temple, M.D. /S/
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Actelion Ltd.
Attention: Thomas W. Lategan, D.Phil.
56 Huckleberry Lane
North Andover, MA 01845

15 pages redacted from this section of the approval package consisted of draft labeling