DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21290/S-020

SUPPLEMENT APPROVAL

Actelion Ltd.
Attention: Dr. Allen D. Nickol
Associate Director, Drug Regulatory Affairs
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

Dear Dr. Nickol:

Please refer to your Supplemental New Drug Application (sNDA) dated December 21, 2010, received December 21, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tracleer (bosentan) 62.5 and 125 mg tablets.

We also acknowledge receipt of your amendments dated June 17, July 1, July 15, September 13, October 17 and 24, 2011 and April 23, June 28, August 24, and September 5, 2012; and your risk evaluation and mitigation strategy (REMS) assessment dated January 18, 2012. The June 17, 2011, submission constituted a complete response to our April 21, 2011, action letter.

This sNDA provides for several proposed REMS modifications to support marketing of a new blister pack presentation of Tracleer (bosentan) 62.5 and 125 mg tablets for hospital use. This sNDA also provides for revisions to the labeling for Tracleer (bosentan) tablets.

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

LABELING CHANGES

General comments:

- the term "liver injury" was changed to "hepatotoxicity"
- the term "liver function" was changed to "serum aminotransferases"
- the proprietary and established drug names were switched (i.e., "bosentan" versus "Tracleer") depending on the context for use
- minor revisions to reflect active voice

In the **HIGHLIGHTS** section of the package insert:

Revised text in the **BOXED WARNING**
FROM

Tracleer can be prescribed and dispensed only through a restricted distribution program (Tracleer Access Program) because of these risks:
TO
Tracleer is available only through a restricted distribution program called the Tracleer Access Program (T.A.P.) because of these risks (5.2):

Revised text in **DOSAGE FORMS AND STRENGTHS**
FROM
62.5 mg and 125 mg unscored tablets (3)
TO
Tablet: 62.5 mg and 125 mg (3)

Revised text in **WARNINGS AND PRECAUTIONS**
FROM

- Pre-existing hepatic impairment: Avoid use in moderate and severe impairment. Use with caution in mild impairment (5.2).
- Fluid retention: May require intervention (5.3).
- Decreased sperm counts: it cannot be excluded that endothelin receptor antagonists such as Tracleer have an adverse effect on spermatogenesis. (5.4)
- Decreases in hemoglobin and hematocrit: Monitor hemoglobin levels after 1 and 3 months of treatment, then every 3 months thereafter (5.5).
- Pulmonary veno-occlusive disease: If signs of pulmonary edema occur, consider the possibility of underlying pulmonary veno-occlusive disease and discontinue treatment if necessary (5.6).

TO

- Pre-existing hepatic impairment: Avoid use in moderate and severe impairment. Use with caution in mild impairment (5.3).
- Fluid retention: May require intervention (5.4).
- Pulmonary veno-occlusive disease *(*PVOD*)*: If signs of pulmonary edema occur, consider the diagnosis of associated PVOD and consider discontinuing Tracleer (5.5)
- Decreased sperm counts (5.6)
- Decreases in hemoglobin and hematocrit: Monitor hemoglobin levels after 1 and 3 months of treatment, then every 3 months thereafter (5.7).

Revised text in **ADVERSE REACTIONS**
FROM
Most common (≥3%) placebo-adjusted adverse reactions are respiratory tract infection and anemia (6.1).
TO
Common adverse reactions (≥3% more than placebo) are respiratory tract infection and anemia (6.1).

Revised text in **DRUG INTERACTIONS**
FROM

- Hormonal contraceptives: Use with Tracleer decreases exposure and reduces contraceptive effectiveness (7.2).
- Cyclosporine A, glyburide: Concomitant administration of each drug with Tracleer is contraindicated (7.3, 7.4).
- Simvastatin and other CYP3A-metabolized statins: Combination use decreases statin levels and may reduce efficacy (7.6).
- Rifampin: Alters bosentan levels. Monitor hepatic function weekly for 4 weeks, followed by normal monitoring (7.7).

TO

- Hormonal contraceptives: Tracleer use decreases contraceptive exposure and reduces effectiveness (7.2).
- Simvastatin and other CYP3A-metabolized statins: Combination use decreases statin exposure and may reduce efficacy (7.6).
- Rifampin: Alters bosentan exposure. Monitor hepatic function weekly for 4 weeks, followed by normal monitoring (7.7).

Revised text in **USE IN SPECIFIC POPULATIONS**
FROM
Nursing mothers: Discontinue nursing or the drug taking into consideration the importance of the drug to the mother (8.3).
TO
Nursing mothers: Choose breastfeeding or Tracleer (8.3).

Revised text under **RECENT MAJOR CHANGES**

Revised the **Table of Contents** to reflect updated labeling text.

In the **FULL PRESCRIBING INFORMATION** section of the package insert:

Revised text in the **BOXED WARNING**
FROM
Because of the risk of liver injury and birth defects, Tracleer is available only through a special restricted distribution program called the Tracleer Access Program (T.A.P.), by calling 1 866 228 3546. Only prescribers and pharmacies registered with T.A.P. may prescribe and distribute Tracleer. In addition, Tracleer may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P. *[see Warnings and Precautions (5.7)]*.
TO
Because of the risks of hepatotoxicity and birth defects, Tracleer is available only through a restricted program called the Tracleer Access Program (T.A.P.). T.A.P. is a component of the Tracleer Risk Evaluation and Mitigation Strategy (REMS). Under the Tracleer REMS, prescribers, patients, and pharmacies must enroll in the program *[see Warnings and Precautions (5.2)]*.

Revised text in **DOSAGE AND ADMINISTRATION**
ADDED
Healthcare professionals who prescribe Tracleer must enroll in the Tracleer Access Program (T.A.P.) and must comply with the required monitoring to minimize the risks associated with Tracleer *[see Warnings and Precautions (5.2)]*.

COMBINED SECTIONS 2.2 AND 2.3
Revised text reads

2.2 Dosage Adjustments for Patients Developing Aminotransferase Elevations

Measure liver aminotransferase levels prior to initiation of treatment and then monthly. If aminotransferase levels increase, revise the monitoring and treatment plan. The table below summarizes the dosage adjustment and monitoring recommendations for patients who develop aminotransferase elevations >3 X ULN during therapy with Tracleer. Discontinue Tracleer if liver aminotransferase elevations are accompanied by clinical symptoms of hepatotoxicity (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN. There is no experience with the reintroduction of Tracleer in these circumstances.

To reduce redundancy with other sections in the PI, SECTIONS 2.4 AND 2.5 were removed

Revised text in **DOSAGE FORMS AND STRENGTHS**
FROM

Tracleer is available as 62.5 mg and 125 mg film-coated, unscored tablets for oral administration.

62.5 mg tablets: film-coated, round, biconvex, orange-white tablets, embossed with identification marking “62,5”

125 mg tablets: film-coated, oval, biconvex, orange-white tablets, embossed with identification marking “125”

TO

62.5 mg and 125 mg film-coated, tablets for oral administration.

62.5 mg tablets: round, biconvex, orange-white tablets, embossed with identification marking “62,5”

125 mg tablets: oval, biconvex, orange-white tablets, embossed with identification marking “125”

Revised text in **CONTRAINDICATIONS/Pregnancy**
FROM

Use of Tracleer is contraindicated in females who are or may become pregnant. While there are no adequate and well controlled studies in pregnant females, animal studies show that Tracleer is likely to cause major birth defects when administered during pregnancy. In animal studies, bosentan caused teratogenic effects including malformations of the head, mouth, face, and large blood vessels. Therefore, pregnancy must be excluded before the start of treatment with Tracleer. Throughout treatment and for one month after stopping Tracleer, females of child bearing potential must use two reliable methods of contraception unless the patient has a tubal sterilization or Copper T 380A IUD or LNg 20 IUS inserted, in which case no other contraception is needed. Monthly pregnancy tests should also be obtained. If this drug is used during pregnancy or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. *[see Use in Specific Populations (8.1)]*.

TO
Use of Tracleer is contraindicated in females who are or may become pregnant. To prevent pregnancy, females of childbearing potential must use two reliable forms of contraception during treatment and for one month after stopping Tracleer *[see Boxed Warning, Drug Interactions (7.2), Use in Specific Populations (8.1)]*.

Revised text in **WARNINGS AND PRECAUTIONS/Hepatotoxicity**
FROM
Elevations in ALT or AST by more than 3 x ULN were observed in 11% of bosentan-treated patients (N = 658) compared to 2% of placebo-treated patients (N = 280). Three-fold increases were seen in 12% of 95 pulmonary arterial hypertension (PAH) patients on 125 mg twice daily and 14% of 70 PAH patients on 250 mg twice daily. Eight-fold increases were seen in 2% of PAH patients on 125 mg twice daily and 7% of PAH patients on 250 mg twice daily. Bilirubin increases to ≥3 x ULN were associated with aminotransferase increases in 2 of 658 (0.3%) of patients treated with bosentan. The combination of hepatocellular injury (increases in aminotransferases of > 3 x ULN) and increases in total bilirubin (≥ 3 x ULN) is a marker for potential serious liver injury. Elevations of AST and/or ALT associated with bosentan are dose-dependent, occur both early and late in treatment, usually progress slowly, are typically asymptomatic, and usually have been reversible after treatment interruption or cessation. Aminotransferase elevations also may reverse spontaneously while continuing treatment with Tracleer. Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN, treatment should be stopped. There is no experience with the re-introduction of Tracleer in these circumstances *[see Dosage and Administration (2.2)]*.

TO
Elevations in ALT or AST by more than 3 x ULN were observed in 11% of Tracleer-treated patients (n = 658) compared to 2% of placebo-treated patients (n = 280). Three-fold increases were seen in 12% of 95 pulmonary arterial hypertension (PAH) patients on

125 mg twice daily and 14% of 70 PAH patients on 250 mg twice daily. Eight-fold increases were seen in 2% of PAH patients on 125 mg twice daily and 7% of PAH patients on 250 mg twice daily. Bilirubin increases to ≥3 x ULN were associated with aminotransferase increases in 2 of 658 (0.3%) of patients treated with Tracleer. The combination of hepatocellular injury (increases in aminotransferases of > 3 x ULN) and increases in total bilirubin (≥ 2x ULN) is a marker for potential serious hepatotoxicity. Elevations of AST or ALT associated with Tracleer are dose-dependent, occur both early and late in treatment, usually progress slowly, are typically asymptomatic, and usually have been reversible after treatment interruption or cessation. Aminotransferase elevations also may reverse spontaneously while continuing treatment with Tracleer. Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly and therapy adjusted accordingly *[see Dosage and Administration (2.2)]*. Discontinue Tracleer if liver aminotransferase elevations are accompanied by clinical symptoms of hepatotoxicity (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN.

Revised text in **WARNINGS AND PRECAUTIONS/Prescribing and Distribution Program for Tracleer** (note: 5.7 was moved to 5.2 which affected the numbering of the other subsections as well)

FROM

Because of the risks of liver injury and birth defects, Tracleer is available only through a special restricted distribution program called the Tracleer Access Program (T.A.P.). Only prescribers and pharmacies registered with T.A.P. may prescribe and distribute Tracleer. In addition, Tracleer may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P. Information about Tracleer and T.A.P. can be obtained by calling 1-866-228-3546.

To enroll in T.A.P., prescribers must complete the T.A.P. Tracleer (bosentan) Enrollment and Renewal Form (see T.A.P. Tracleer (bosentan) Enrollment and Renewal Form for full prescribing physician agreement) indicating agreement to:

- Read and understand the communication and educational materials for prescribers regarding the risks of Tracleer.
- Review and discuss the Tracleer Medication Guide and the risks of bosentan (including the risks of teratogenicity and hepatotoxicity) with every patient prior to prescribing Tracleer.
- Review pretreatment liver function tests (ALT/AST/bilirubin) and, for females of childbearing potential, confirm that the patient is not pregnant.
- Agree to order and monitor monthly liver function tests and, for females of childbearing potential, pregnancy tests.
- Enroll all patients in T.A.P. and renew patients' enrollment annually thereafter.
- Educate and counsel females of childbearing potential to use reliable contraception, as defined on the Tracleer Enrollment and Renewal Form, during treatment with Tracleer and for one month after treatment discontinuation.
- Counsel patients who fail to comply with the program requirements.

- Notify Actelion Pharmaceuticals US, Inc. of any adverse events, including liver injury, and report any pregnancy during Tracleer treatment.

Throughout treatment and for one month after stopping Tracleer, females of childbearing potential must use two reliable methods of contraception unless the patient has a tubal sterilization or Copper T 380A IUD or LNg 20 IUS inserted, in which case no other contraception is needed. 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.

TO
Because of the risks of hepatotoxicity and birth defects, Tracleer is available only through a restricted program called the Tracleer Access Program (T.A.P.) [see Boxed Warning and Contraindications (4.1)]. As a component of the Tracleer REMS, prescribers, patients, and pharmacies must enroll in the program.

Required components of the Tracleer REMS are:
- Healthcare professionals who prescribe Tracleer must review the prescriber educational materials, enroll in T.A.P. and comply with its requirements.
- Healthcare professionals must (1) review serum aminotransferases (ALT/AST) and bilirubin, and agree to order and monitor these tests monthly; and (2) for females of childbearing potential, confirm that the patient is not pregnant, and agree to order and monitor pregnancy tests monthly.
- To receive Tracleer, all patients must understand the risks and benefits, complete a patient enrollment form, and be re-enrolled annually by their prescriber.
- Pharmacies that dispense Tracleer must enroll in the program and agree to comply with the T.A.P. requirements.

Further information about Tracleer and T.A.P. is available at www.tracleerrems.com or 1-866-228-3546.

Revised text in **WARNINGS AND PRECAUTIONS/Patients with pre-existing hepatic impairment**
FROM
Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. Tracleer should generally be avoided in patients with moderate or severe liver impairment *[see Dosage and Administration (2.5)]*. In addition, Tracleer should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) because monitoring liver injury in these patients may be more difficult *[see Boxed Warning]*.

TO
Tracleer is not recommended in patients with moderate or severe liver impairment *[see Dosage and Administration (2.2)]*. In addition, Tracleer should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) prior to drug initiation because

monitoring hepatotoxicity in these patients may be more difficult *[see Boxed Warning, Use in Specific Populations (8.6)]*.

Minor revisions to the text in **WARNINGS AND PRECAUTIONS/Pulmonary veno-occlusive disease**

Most of the text that was in **WARNINGS AND PRECAUTIONS/Decreased sperm counts** and **WARNINGS AND PRECAUTIONS/Decreases in hemoglobin and hematocrit** was moved to **ADVERSE REACTIONS/Decreased sperm counts and ADVERSE REACTIONS/Decrease in hemoglobin and hematocrit**.

Revised text in **USE IN SPECIFIC POPULATIONS/Geriatric use**
FROM
Clinical studies of Tracleer did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Clinical experience has not identified differences in responses between elderly and younger patients. In general, caution should be exercised in dose selection for elderly patients given the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group.

TO
Clinical studies of Tracleer did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

Deleted the heading **USE IN SPECIFIC POPULATIONS/Patients with low body weight** (because this section included a reference to another section of the PI but no additional information).

Switched the order (but not the wording) of the two paragraphs in **CLINICAL PHARMACOLOGY/Mechanism of action**.

Revised text in **HOW SUPPLIED/STORAGE AND HANDLING**
FROM
62.5 mg film-coated, round, biconvex, orange-white tablets, embossed with identification marking “62,5”, packaged in a white high-density polyethylene bottle and a white polypropylene child-resistant cap.
NDC 66215-101-06: Bottle containing 60 tablets.

125 mg film-coated, oval, biconvex, orange-white tablets, embossed with identification marking “125”, packaged in a white high-density polyethylene bottle and a white polypropylene child-resistant cap.
NDC 66215-102-06: Bottle containing 60 tablets.

TO

62.5 mg film-coated, round, biconvex, orange-white tablets, embossed with identification marking “62,5”, packaged in a white high-density polyethylene bottle and a white polypropylene child-resistant cap or in foil blister-strips for hospital unit-dosing.
NDC 66215-101-06: Bottle containing 60 tablets.
NDC 66215-101-03: Carton of 30 tablets in 10 blister strips of 3 tablets.

125 mg film-coated, oval, biconvex, orange-white tablets, embossed with identification marking “125”, packaged in a white high-density polyethylene bottle and a white polypropylene child-resistant cap or in foil blister-strips for hospital unit-dosing.
NDC 66215-102-06: Bottle containing 60 tablets.
NDC 66215-102-03: Carton of 30 tablets in 10 blister strips of 3 tablets.

Revised text in **PATIENT COUNSELING INFORMATION**
FROM
Advise patients to consult the Medication Guide on the safe use of Tracleer *[see Medication Guide (17.2)]*.

17.1 Important Information

Monthly monitoring of serum aminotransferases
The physician should discuss with the patient the importance of monthly monitoring of serum aminotransferases.
Pregnancy testing and avoidance of pregnancy
Patients should be advised that Tracleer is likely to cause birth defects based on animal studies. Tracleer treatment should only be initiated in females of childbearing potential following a negative pregnancy test. Females of childbearing potential must have monthly pregnancy tests and need to use two different forms of contraception while taking Tracleer and for one month after discontinuing Tracleer. Females who have a tubal ligation or a Copper T 380A IUD or LNg 20 IUS can use these contraceptive methods alone. Patients should be instructed to immediately contact their physician if they suspect they may be pregnant and should seek contraceptive advice from a gynecologist or similar expert as needed.

Drug Interactions
The physician should discuss with the patient possible drug interactions with Tracleer, and which medications should not be taken with Tracleer. The physician should discuss the importance of disclosing all concomitant or new medications.

17.2 Medication Guide

See accompanying Medication Guide

TO
See FDA-approved patient labeling (Medication Guide)
Restricted access
Advise the patient that Tracleer is only available through a restricted access program called the Tracleer Access Program (T.A.P.)
As a component of the Tracleer REMS, prescribers must review the contents of the Tracleer Medication Guide with the patient before initiating Tracleer.
Instruct patients that the risks associated with Tracleer include:

- **Hepatotoxicity**
  Discuss with the patient the requirement to measure serum aminotransferases monthly.
- **Serious birth defects if used by pregnant women**
  Educate and counsel female patients of child bearing potential about the need to use reliable methods of contraception during treatment with Tracleer and for one month after treatment discontinuation. Females of childbearing potential must have monthly pregnancy tests and must use two different forms of contraception while taking Tracleer and for one month after discontinuing Tracleer. Females who have a tubal ligation or a Copper T 380A IUD or LNg 20 IUS can use these contraceptive methods alone. Patients should be instructed to immediately contact their physician if they suspect they may be pregnant. Patients should seek additional contraceptive advice from a gynecologist or similar expert as needed.

  Advise the patient that Tracleer is available only from specialty pharmacies that are enrolled in Tracleer Access Program.
  Patients must sign the Tracleer Enrollment for Patients and Prescribers form to confirm that they understand the risks of Tracleer.
  Advise patients that they may be requested to participate in a survey to evaluate the effectiveness of the Tracleer REMS.
  Other Risks Associated with Tracleer
  Instruct patients that the risks associated with Tracleer also include the following:
  Decreases in hemoglobin and hematocrit – advise patients of the importance of hemoglobin testing
  Decreases in sperm count
  Fluid retention

In the **MEDICATION GUIDE**:

Under **What is the most important information I should know about TRACLEER?**
Revised the text
FROM
You must have a blood test to check your liver function before you start Tracleer and each month after that.
TO
You must have your blood tested to check your liver function before you start Tracleer and each month after that.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements and any annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for

Content of Labeling Technical Qs and As" at
http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).
We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Tracleer (bosentan) tablets was originally approved on August 7, 2009, and a REMS modification was approved on February 19, 2010. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS consist of the following changes:

- Added requirements for use of Tracleer in an inpatient setting, including prescriber certification, hospital certification, and a description of how inpatient settings will obtain the drug.
- Differentiation between inpatient and outpatient dispensing processes.
- New Dear Healthcare Provider letters for prescribers and hospitals to communicate the availability of a hospital blister, to be distributed within 60 days of approval of the modified REMS.
- Changes to the implementation system to include certified hospitals and plans to monitor compliance with the Tracleer REMS requirements
- Changes to various appended REMS materials including the patient enrollment form to consist of an initial enrollment form and an annual re-enrollment form; and changes to the Prescriber Essentials guide, Patient Essentials guide, monthly reminder for patients, new hospital use communication material, and updates to the Tracleer REMS website landing page for clarification and/or to reflect the revised processes

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed modified REMS, submitted on June 28, 2012, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on February 19, 2010.

The revised REMS assessment plan should include, but is not limited, to the following:

1. Demographic data regarding patients enrolled in the Tracleer Access Program, including, by reporting period and overall:
    a. Total number of patients receiving Tracleer, stratified by age, gender and other demographics
    b. The number of and person-years of exposure
    c. Patient diagnosis
2. The number of and person-years of exposure for female patients of childbearing potential, by reporting period and overall
3. The number of patients with treatment interruptions, and the reasons for those treatment interruptions for the reporting period
4. Numbers, reasons, and lengths in days of shipment delays for the reporting period
5. Number of patients and reasons for dispensing > 30 day supply for the reporting period
    a. An analysis of frequency of dispensing > 30 day supply by pharmacy
    b. An analysis of prescribing > 30 day supply by prescriber and by unique patient (as identified by Actelion Control Number)
6. An analysis of the frequency of prescribing a daily dose > 250 mg per day, by prescriber and by patient for the reporting period
7. The number of times (percent) the patient reported to the pharmacy they had not completed laboratory testing for the reporting period
    a. Monthly pregnancy testing for female patients of childbearing potential by quarter and overall
    b. Liver function testing by quarter and overall
8. The number of times (percent) the patient reported an abnormal test result to the pharmacy for the reporting period
9. The number of times (percent) a shipment was held because the patient reported an abnormal test result to the pharmacy, and the length in days of the delayed shipment for the reporting period

10. The number and reasons for discontinuation for the reporting period and overall

11. An analysis of pregnancies,

    a. pregnancy outcomes for exposed pregnancies, by reporting period and overall

    b. the root-cause analysis of pregnancies in the reporting period to determine the reason the REMS failed to prevent the pregnancy exposure

    c. The number of pregnancy exposures by reporting period and overall (pregnancy exposures will be recorded within the REMS database as well as the global safety database, with appropriate linkage to allow matching of the cases reported in the REMS database to cases in the global safety database)

12. Summary of cases of liver injury, by reporting period and overall, including cases of serum transaminases > 8 X upper limit of normal (ULN); cases of serum transaminases > 3 X ULN accompanied by increases in serum bilirubin ≥ 2 X ULN; and cases of liver injury associated with hospitalization, liver transplant, being listed for liver transplant or death

    a. Analysis of cases of liver injury in the reporting period

13. Summary data on certified prescribers, for the reporting period and overall, including:

    a. Number of certified prescribers

    b. Stratification based on specialty

14. Data and analysis on certified pharmacies, for the reporting period, including but not limited to:

    a. Distribution data from the certified pharmacies

    b. Compliance with liver function and pregnancy testing monitoring data

    c. Distribution and dispensing of the Medication Guide in accordance with 21 CFR§ 208.24

    d. Reports of operational audits, including results of distribution data reconciliation

    e. A Pharmacy Compliance Report including the need for intervention with each certified pharmacy and corrective actions taken to address noncompliance

15. Survey data obtained during the reporting period assessing patient and prescriber understanding of the risks associated with the use of Tracleer

16. An analysis of complaints spontaneously obtained during the reporting period received from patients about the burden of the REMS

17. With respect to REMS goals, an assessment of the extent to which the elements to assure safe use are meeting the goals or whether the goals or such elements should be modified

18. A status report on hospitals certified to dispense Tracleer in the inpatient setting

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 21290 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify submissions containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 021290
REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021290 - PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021290
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

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

If you have any questions, please call Dan Brum, Pharm.D., 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

Enclosures:

Package Insert
Medication Guide
Carton and Container Labeling
Modified REMS
REMS Materials

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN L STOCKBRIDGE
10/02/2012