CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-290/S-001

Administrative Documents

ACTELION
Creative Science for Advanced Medicine

Allschwil, 14 August, 2000

Certification under 21CFR, Section 314.50(h)(1)(3)

To whom it may concern,

Applicant herewith certifies that regarding bosentan it has an exclusive license under all Roche Patent Rights covering the compound (US Patent No.5 292 740) and processes for the manufacture thereof (US Patent No.5 883 254 and corresponding Patent Applications like 09/161 086; 09/526 252; 09/354 943). This exclusive license is also unlimited relative to indications.

Dr. Juliane Bernholz
Vice President Project Management

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EXCLUSIVITY SUMMARY for NDA # 21-290 SUPPL # 001

Trade Name Tracleer Generic Name bosentan

Applicant Name Actelion Ltd. HFD-110

Approval Date October 6, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X__/

   b) Is it an effectiveness supplement? YES /_X__/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE8

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /_X__/ NO /___/

If yes, NDA # 21-290 Drug Name Tracleer (bosentan)

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____
Signature of Preparer Date
Melissa Robb
Regulatory Health Project Manager, HFD-110

_____
Signature of Division Director Date
Douglas C. Throckmorton, M.D.
Director, Division of Cardio-Renal Drug Products, HFD-110

cc:
Archival NDA 21-290
HFD-110/Division File
HFD-110, Melissa Robb/RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Doug Throckmorton
10/6/03 02:22:21 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-290 Supplement Type (e.g. SE5): SE8 Supplement Number: 001

Stamp Date: December 6, 2002 Action Date: October 6, 2003

HFD-110 Trade and generic names/dosage form: Tracleer(bosentan) 62.5 and 125 mg Tablets

Applicant: Actelion Ltd. Therapeutic Class: 1011001, Endothelin Receptor Antagonists

Indication(s) previously approved: Treatment of Pulmonary Arterial Hypertension in patients with WHO Class III or IV symptoms, to improve exercise ability and decrease the rate of clinical worsening.

Note: There are no new indications approved with this supplement. The pediatric requirement was waived for the original NDA because the drug has orphan status.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): None

Indication #1: _____

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	kg____	mo.____	yr.____	Tanner Stage____
Max____	kg____	mo.____	yr.____	Tanner Stage____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns

- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Melissa Robb, HFD-100
Regulatory Project Manager

cc: NDA 21-290
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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

/s/

Melissa Robb

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ACTELION
Creative Science for Advanced Medicine

January 9, 2003

Debarment Certification

Actelion Pharmaceuticals Inc., hereby certifies that we did not and will not use in any capacity the services of any person debarred under Section 306(a) or (b) in connection with this application.

Tom Lutegan

VP, Regulatory Affairs and Medical Information

Actelion Life Sciences Ltd.
1840 Gateway Dr, 2nd Floor San Mateo, CA 94404 USA
Ph: (650) 378-1474 Fax: (650) 378- 1485

Project Manager Overview of NDA 21-290/S-001
Tracleer (bosentan) 62.5 & 125 mg Tablets
October 1, 2003

Background:
Bosentan, an endothelin receptor antagonist, was approved on November 20, 2001 for the treatment of pulmonary arterial hypertension. Actelion is proposing revisions to the current labeling based on completed studies since the drug's approval in November 2001.

Medical Reviews
Dr. Gordon's review dated October 1, 2003 reviews the financial disclosure information provided by the sponsor.

Dr. Gordon's review dated June 4, 2003 included a review of safety and efficacy of studies submitted to support changes in labeling. The proposed changes were based on 3 studies:

1. Protocol AC-052-356, a small uncontrolled trial with 16 patients between the ages of 3 and 16, inclusive
2. Protocol AC-052-301/302, two large placebo controlled trials with a total of 1613 patients with congestive heart failure(this review was a combined medical/statistical review with Dr. Lawrence)
3. Protocol AC-052-355, a small placebo controlled trial evaluating the combined use of bosentan and epoprostenol in patients with primary pulmonary hypertension.

Biopharmaceutical Review
Dr. Hinderling's review dated September 30, 2003 includes a labeling recommendation for the PRECAUTIONS section of the PI to describe the possible interaction of tacrolimus and bosentan.

Dr. Hinderling's reviews dated May 20 and 22, 2003, include reviews of five studies. Of these 5 studies, 3 provided new pharmacokinetic (PK) information and the remaining two studies represent repetitions of earlier performed drug-drug interaction studies of bosentan with ketoconazole and simvastatin. Dr. Hinderling concluded that the only new findings that should be described in labeling are the findings that characterize the PK of bosentan in the adult population with PAH and the findings that characterize the PK of bosentan after oral administration in patients with mild liver impairment. Dr. Hinderling did not believe that any pediatric PK information should be inserted in the label. Dr. Hinderling's review also includes labeling recommendations.

Dr. Hinderling's review dated February 5, 2003 includes a review of the initial application to determine if it is filable.

RPM Review of Labeling

1. Throughout the label the drug name has been changed from TRACLEER™ to TRACLEER®.

2. In the **CLINICAL PHARMACOLOGY/Pharmacokinetics/General** section, the phrase "in healthy adult subjects" has been added to the end of the first sentence.

3. In the **CLINICAL PHARMACOLOGY/Pharmacokinetics/General** section, the second sentence has been changed from:

   Pharmacokinetics of bosentan was not studied in patients with pulmonary arterial hypertension, but exposure is expected to be greater in such patients because increased (30-405) bosentan exposure was observed in patients with severe chronic heart failure.

   To:

The exposure to bosentan after intravenous and oral administration is about 2-fold greater in adult patients with pulmonary arterial hypertension than in healthy adult subjects.

4. In the **CLINICAL PHARMACOLOGY/Pharmacokinetics/Metabolism and Elimination** section, the third and fourth sentences have been changed from:

   Total clearance after a single intravenous dose is about 8 L/hr. Upon multiple dosing, plasma concentrations decrease gradually to 50-65% of those seen after single dose administration, probably the effect of auto-induction of the metabolizing liver enzymes.

   To:

   Total clearance after a single intravenous dose is about 4 L/hr in patients with pulmonary arterial hypertension. Upon multiple oral dosing, plasma concentrations in healthy adults decrease gradually to 50-65% of those seen after single dose administration, probably the effect of auto-induction of the metabolizing liver enzymes.

5. The **CLINICAL PHARMACOLOGY/Pharmacokinetics/Special Populations/***Liver Function Impairment* section has been changed from:

   [

   ]

   To:

   In vitro and *in vivo* evidence showing extensive hepatic metabolism of bosentan suggests that liver impairment could significantly increase exposure of bosentan. In a study comparing 8 patients with mild liver impairment (as indicated by the Child-Pugh method) to 8 controls, the single- and multiple -dose pharmacokinetics of bosentan were not altered in patients with mild hepatic impairment. The influence of moderate or severe liver impairment on the pharmacokinetics of bosentan has not been evaluated. Bosentan should generally be avoided in patients with moderate or severe liver abnormalities and/or elevated aminotransferases > 3 x ULN (See **DOSAGE AND ADMINISTRATION & WARNINGS**).

6. The subsection heading "*Pulmonary Arterial Hypertension*" has been added at the beginning of the **CLINICAL PHARMACOLOGY/Clinical Studies** section.

7. The following has been deleted at the end of the **CLINICAL PHARMACOLOGY/Clinical Studies/***Pulmonary Arterial Hypertension*/Symptoms and Functional Status section:

   The long-term effect of TRACLEER™ was further assessed in an open-label study with 29 patients receiving at least one year of treatment. Without a control group, these data must be interpreted cautiously. During this period, no patients died and one patient deteriorated, requiring treatment with epoprostenol.

8. The following subsection has been added at the end of the **CLINICAL PHARMACOLOGY/Clinical Studies** section:

   Congestive Heart Failure (CHF)
   In a pair of studies, 1613 subjects with NYHA Class III-IV heart failure, left ventricular ejection fraction <35%, on diuretics, ACE inhibitor, and other therapies, were randomized to placebo or TRACLEER® (62.5 mg bid titrated as tolerated to 125 mg bid) and followed for up to 70 weeks.

Use of TRACLEER® was associated with no benefit on patient global assessment (the primary end point) or mortality. However, hospitalizations for heart failure were more common during the first 4 to 8 weeks after bosentan was initiated. Based on these results, bosentan is not effective in the treatment of congestive heart failure with left ventricular dysfunction.

9. The following subsection has been added to the **PRECAUTIONS** section, following *Hematologic Changes*:

   Fluid retention
   In a placebo controlled trial of patients with severe chronic heart failure, there was an increased incidence of hospitalization for CHF associated with weight gain and increased leg edema during the first 4-8 weeks of treatment with TRACLEER®. In addition, there have been numerous post-marketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks after starting TRACLEER®. Patients required intervention with a diuretic, fluid management, or hospitalization for decompensating heart failure (see **CLINICAL STUDIES**; *Congestive Heart Failure*).

10. The following subsection has been added to the **PRECAUTIONS/Drug Interactions** section:

    Tacrolimus: Co-administration of tacrolimus and bosentan has not been studied in man. Co-administration of tacrolimus and bosentan resulted in markedly increased plasma concentrations of bosentan in animals. Caution should be exercised if tacrolimus and bosentan are used together.

11. The following paragraph has been added at the end of the **ADVERSE REACTIONS/Adverse Events** subsection:

    There have been several post-marketing reports of angioneurotic edema associated with the use of bosentan. The onset of the reported cases occurred within a range of 8 hours to 21 days after starting therapy. Some patients were treated with an antihistamine and their signs of angioedema resolved without discontinuing TRACLEER®.

12. The following subsection has been added at the end of the **ADVERSE REACTIONS** section:

    Long-term Treatment
    The long term follow-up of the patients who were treated with TRACLEER® in the two pivotal studies and their open-label extensions (N=235) shows that 93% and 84% of patients were still alive at 1 and 2 years, respectively, after the start of treatment with TRACLEER®. These estimates may be influenced by the presence of epoprostenol treatment, which was administered to 43/235 patients. Without a control group, these data must be interpreted cautiously and cannot be interpreted as an improvement in survival.

13. In the **DOSAGE AND ADMINISTRATION/Dosage Adjustment in Hepatically Impaired Patients** section, the first two sentences have been changed from:

    The influence of liver impairment on the pharmacokinetics of TRACLEER™ has not been evaluated. Because there is *in vivo* and *in vitro* evidence that the main route of excretion of TRACLEER™ is biliary, liver impairment would be expected to increase exposure (Cmax, AUC) to bosentan.

    To:

    Because there is in vitro and in vivo evidence that the main route of excretion of bosentan is biliary, liver impairment could be expected to increase exposure (Cmax and AUC) of bosentan. Mild liver impairment was shown not to impact the pharmacokinetics of bosentan. The influence of moderate or severe liver impairment on the pharmacokinetics of TRACLEER® has not been evaluated.

14. The following manufactured, distributed and marketed information has been added at the end of the label:

    Manufactured by:
    Patheon, Inc.
    Mississauga, Ontario, L5N 7K9, CANADA

    Distributed by:
    ICS
    Louisville, KY40229, USA

    Marketed by:
    Actelion Pharmaceuticals US, Inc.,
    South San Francisco, CA 94080, USA

15. The Medication Guide has been added at the end of the prescribing information.

16. The following changes have been made to the Medication Guide:

    a. In the section "**Who should not take Tracleer?**", in the second section of bullets the following bullet has been added:

        - tacrolimus (used to prevent rejection liver or kidney transplants)

    b. In the section "**What should I avoid while taking Tracleer?**", the fourth bullet has been changed from:

        - **Do not take cyclosporine-A or glyburide.** These medicines can cause too much Tracleer in your blood and increase your chance of liver damage.

        To:

        - **Do not take cyclosporine-A.** This medicine can cause too much Tracleer in your blood and increase your chance of liver damage.
        - **Do not take glyburide.** This medicine can increase your chance of liver damage.

Project Manager's Summary

To my knowledge, there are no issues that might prevent action on this supplement.

Melissa Robb, RHPM

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/s/

Melissa Robb
10/6/03 02:17:23 PM
CSO

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

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-290	Efficacy Supplement Type SE-8	Supplement Number 001	
Drug: Tracleer (bosentan) 62.5 and 125 mg Tablets		Applicant: Actelion Ltd.	
RPM: Melissa Robb		HFD-110	Phone # 301-594-5313
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): N/A	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	N/A
• Other (e.g., orphan, OTC)	Orphan
❖ User Fee Goal Dates	October 6, 2003
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	( ) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	(X) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	N/A 21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	N/A ( ) Verified
❖ Exclusivity Summary (approvals only)	X

❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	Project Manager 10/6/03
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	N/A
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	N/A
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	Filing Meeting: 1/16/03
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	N/A
❖ Clinical review(s) *(indicate date for each review)*	June 4, 2003
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) *(indicate date for each review)*	N/A
❖ Biopharmaceutical review(s) *(indicate date for each review)*	February 5, 2003 May 20, 2003 May 22, 2003 September 30, 2003
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	N/A
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	N/A
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	N/A Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	N/A ( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

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

/s/

Melissa Robb
10/6/03 02:23:31 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-290 Supplement # 001 SE8

Trade Name: Tracleer
Generic Name: bosentan
Strengths: 62.5 and 125 mg Tablets

Applicant: Actelion Ltd

Date of Application: December 4, 2002
Date of Receipt: Decemebr 6, 2002
Date clock started after UN: N/A
Date of Filing Meeting: January 16, 2003
Filing Date: February 4, 2003
Action Goal Date (optional): N/A User Fee Goal Date: October 6, 2003

Indication(s) requested:

No new indications requested. Actelion is proposing revisions to the current labeling based on completed studies since the approval of Tracleer in November 2001.

Type of Application: Original (b)(1) NDA _____ Original (b)(2) NDA _____
(b)(1) Supplement ____X____ (b)(2) Supplement _____
[If the Original NDA was a (b)(2), all supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or a (b)(2).]

NOTE: If the application is a 505(b)(2) application, complete the 505(b)(2) section at the end of this summary.

Therapeutic Classification: S ___X_____ P _____
Resubmission after a withdrawal? ____NO_____ Resubmission after a refuse to file? ___NO_____
Chemical Classification: (1,2,3 etc.) ____N/A_____
Other (orphan, OTC, etc.) __Orphan_____

User Fee Status: Paid ___N/A_____ Waived (e.g., small business, public health) ___N/A_____
Exempt (orphan, government) ___X_____
Form 3397 (User Fee Cover Sheet) submitted: YES
User Fee ID # N/A
Clinical data? YES ___X_____ NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES

If yes, explain:

Bosentan was approved on November 20, 2001 still under 7-year exclusivity as an orphan drug.

Does another drug have orphan drug exclusivity for the same indication? NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

N/A

Is the application affected by the Application Integrity Policy (AIP)? NO
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? N/A

- Does the submission contain an accurate comprehensive index? YES
- Was form 356h included with an authorized signature? YES
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES
  If no, explain:

- If an electronic NDA, does it follow the Guidance? YES
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Cover Letter-also in hard copy
  356h-also in hard copy
  Labeling
  Study reports

  Additional comments:

- If in Common Technical Document format, does it follow the guidance? N/A

- Is it an electronic CTD? NO
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- Patent information included with authorized signature? YES

- Exclusivity requested? NO
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure information included with authorized signature? YES
  (Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? N/A

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
  YES

- List referenced IND numbers:

  58,317
  [ ]

- End-of-Phase 2 Meeting(s)? NO
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? NO
  If yes, distribute minutes before filing meeting.

Project Management

- Package insert consulted to DDMAC? YES

- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? N/A

- MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support?
  N/A

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?

N/A

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of Surveillance, Research and Communication Support?

  N/A

- Has DOTCDP been notified of the OTC switch application? N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?

  N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? N/A
  If no, did applicant submit a complete environmental assessment? N/A
  If EA submitted, consulted to Nancy Sager (HFD-357)? N/A

- Establishment Evaluation Request (EER) submitted to DMPQ? N/A

- If parenteral product, consulted to Microbiology Team (HFD-805)? N/A

If 505(b)(2) application, complete the following section: N/A

- Name of listed drug(s) and NDA/ANDA #:

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

  YES NO

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

  ____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

  ____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

  ____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
  ____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:

  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES NO

  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    YES NO

  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    N/A YES NO

  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    N/A YES NO

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

  YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

  YES NO

- EITHER
  The number of the applicant's IND under which the studies essential to approval were conducted.

  YES, IND # _____ NO

  OR
  A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

  N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

  YES NO

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 16, 2003

BACKGROUND:

This is a supplement to an already approved NDA for labeling changes based on completed studies since approval in November 2001.

ATTENDEES:

Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Maryann Gordon, M.D.	Medical Officer, HFD-110
James Hung, Ph.D.	Statistical Team Leader, HFD-710
Peter Hinderling, M.D.	Pharmacokineticist, HFD-860
John Koerner, Ph.D.	Pharmacologist, HFD-110
Robert Shibuya, Ph.D.	Division of Scientific Investigations, HFD-47
Zelda McDonald	Chief, Project Management Staff, HFD-110
Melissa Robb	Regulatory Health Project Manager, HFD-110

ASSIGNED REVIEWERS:

Discipline	Reviewer	To be completed by
Medical:	Maryann Gordon, M.D.	2/28/03
Biopharmaceutical:	Peter Hinderling, M.D.	5/31/03
Regulatory Project Manager:	Melissa Robb	

Per reviewers, are all parts in English or English translation? YES
If no, explain:

CLINICAL FILE __X__ REFUSE TO FILE ____

- Clinical site inspection needed: NO
- Advisory Committee Meeting needed? NO

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A

CLINICAL MICROBIOLOGY N/A

STATISTICS FILE __X__ REFUSE TO FILE ____

BIOPHARMACEUTICS FILE __X__ REFUSE TO FILE ____

- Biopharm. inspection needed: NO

PHARMACOLOGY FILE __X___ REFUSE TO FILE _____

- GLP inspection needed: NO

CHEMISTRY FILE __X___ REFUSE TO FILE _____

- Establishment(s) ready for inspection? N/A
- Microbiology N/A

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

___X____ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

___X____ No filing issues have been identified.

__N/A_____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

_____
Melissa Robb
Regulatory Project Manager, HFD-110

Drafted: 1/17/03 Finaled: 1/22/03

RD:

Throckmorton	1/21/03
Stockbridge	1/21/03
McDonald	1/21/03
Gordon	1/21/03
Hung	1/21/03
Hinderling	1/21/03
Koerner	1/21/03
Shibuya	1/17/03

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/s/

Melissa Robb
1/22/03 07:34:27 AM
CSO

Memo to file
NDA#21,290

Evaluation of Financial Disclosure
The sponsor has declared that they have not entered into any financial arrangement with the clinical investigators (list attached) involved in the conduct of study AC-052-355 whereby the value of compensation to the investigator could be affected by the outcome of the studies.

The following individuals participated in the BREATHE 2 and BREATHE 3 studies. Financial disclosures are on file for the individuals listed. Investigators who participated in the ENABLE study are not listed since the data provided by ENABLE are not provided to support an efficacy claim. However, financial disclosure documents are on file for the ENABLE investigators.

Name	Study	Site	Role (PI, Subinvestigator, Coordinator)	FDA 3455 (Y/N/Equivalent)
			Subinvestigator	Y
David B. Badesch, MD	AC-052-355	102	PI	Y
			Subinvestigator	Y
Robyn J. Barst, MD	AC-052-355	112	PI	Y
			Subinvestigator	Y
Dr. Anco Boonstra	AC-052-355	210	PI	Y
Richard N. Channick, MD	AC-052-355	101	PI	Y
			Subinvestigator	Y
			Subinvestigator	Y
Adaani Frost, MD	AC-052-355	106	PI	Y
Dr. Nazzareno Galie	AC-052-355	208	PI	Y
			Subinvestigator	Y
			Subinvestigator	Y
			Subinvestigator	Y
			Subinvestigator	Y
			Subinvestigator	Y
			Subinvestigator	Y
			Subinvestigator	Y
			Subinvestigator	Y
Valerie V. McLaughlin, MD	AC-052-355	117	PI	Y

			Coordinator	Y
			Subinvestigator	Y
			Subinvestigator	Y
			Subinvestigator	Y
			Subinvestigator	Y
Ivan M. Robbins, MD	AC-052-355	105	PI	Y
			Subinvestigator	Y
			Subinvestigator	Y
			Subinvestigator	Y
G Simonneau, MD	AC-052-355	201	PI	Y
			Subinvestigator	Y
			Subinvestigator	Y
			Coordinator	Y
			Coordinator	Y
			Subinvestigator	Y
			Subinvestigator	Y
Robyn J. Barst, MD	AC-052-356	01	PI	Y
			Subinvestigator	Y
			Subinvestigator	Y
			Subinvestigator	Y
D. Dunbar Ivy, MD	AC-052-356	02	PI	Y
[redacted]	[redacted]		Subinvestigator	Y
			Coordinator	Y
			Subinvestigator	Y
			Coordinator	Y
			Coordinator	Y

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/s/

Maryann Gordon

10/1/03 02:02:59 PM

MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: June 30, 2002

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
ANDREW OAKLEY	CHIEF FINANCIAL OFFICER
FIRM / ORGANIZATION	
ACTELION PHARMACEUTICALS LTD.	
SIGNATURE	DATE
	8-1-03

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Created by PSC Media Arts Branch (301) 443-2454 EF

The following individuals participated in the BREATHE 2 and BREATHE 3 studies. Financial disclosures are on file for the individuals listed. Investigators who participated in the ENABLE study are not listed since the data provided by ENABLE are not provided to support an efficacy claim. However, financial disclosure documents are on file for the ENABLE investigators.

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			Subinvestigator	Y
Dr. Anco Boonstra	AC-052-355	210	PI	Y
Richard N. Channick, MD	AC-052-355	101	PI	Y
			Subinvestigator	Y
			Subinvestigator	Y
Adaani Frost, MD	AC-052-355	106	PI	Y
Dr. Nazzareno Galie	AC-052-355	208	PI	Y
			Subinvestigator	Y
			Subinvestigator	Y
			Subinvestigator	Y
			Subinvestigator	Y
			Subinvestigator	Y
			Subinvestigator	Y
			Subinvestigator	Y
			Subinvestigator	Y
Valerie V. McLaughlin, MD	AC-052-355	117	PI	Y

			Coordinator	Y
			Subinvestigator	Y
			Subinvestigator	Y
			Subinvestigator	Y
			Subinvestigator	Y
Ivan M. Robbins, MD	AC-052-355	105	PI	Y
			Subinvestigator	Y
			Subinvestigator	Y
			Subinvestigator	Y
G. Simonneau, MD	AC-052-355	201	PI	Y
			Subinvestigator	Y
			Subinvestigator	Y
			Coordinator	Y
			Coordinator	Y
			Subinvestigator	Y
			Subinvestigator	Y
Robyn J. Barst, MD	AC-052-356	01	PI	Y
			Subinvestigator	Y
			Subinvestigator	Y
			Subinvestigator	Y
D. Dunbar Ivy, MD	AC-052-356	02	PI	Y
			Subinvestigator	Y
[redacted]	[redacted]	[redacted]	Coordinator	Y
			Subinvestigator	Y
			Coordinator	Y
			Coordinator	Y

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved OMB No
Expiration Date: February 2

USER FEE COVER SHEE

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions reverse side If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fe can be found on CDER s website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Actelion Ltd
Gewerbestrasse 16
Allschwil, CH-4123
SWITZERLAND

2 TELEPHONE NUMBER *(Include Area Code)*

(011) 41 61 487 4545

3 PRODUCT NAME

Tracleer® (bosentan) Tablets

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

21-290

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP AND SIGN THIS FORM

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICAT

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO

(APPLICATION NO. CONTAINING THE DATA).

6 USER FEE I.D. NUMBER

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☒ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8 HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☐ NO
(See item 8, reverse side if answered YES)

ublic reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing structions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. and comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

partment of Health and Human Services
od and Drug Administration
ER, HFM-99
01 Rockville Pike
kville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Thomas Lutz	VP, Regulatory Affairs	12/19/02

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-290/S-001

Acetelion Ltd.
Attention: Peter Hermann, Ph.D.
Vice President, Regulatory Affairs & Medical Information
Gewerbestrasse 16
Allschwil, CH-4123
Switzerland

Dear Dr. Hermann:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Tracleer (bosentan) Tablets

NDA Number: 21-290

Supplement number: 001

Review Priority Classification: Standard

Date of supplement: December 4, 2002

Date of receipt: December 6, 2002

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 4, 2003in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 6, 2003.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Document Room 5002
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Document Room 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any question, please contact:

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

Sincerely,

/S/

Zelda McDonald
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

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