CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-290

Administrative Documents

ACTELION
Creative Science for Advanced Medicine

Allschwil, 14 August, 2000

Certification under 21CFR, Section 314.50(h)(i)(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.

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EXCLUSIVITY SUMMARY FOR NDA # __21-290_____ SUPPL #_____

Trade Name ___Tracleer_____ Generic Name _bosentan_____

Applicant Name __Actelion_____ HFD # _110_____

Approval Date If Known _11/20/01_____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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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 question about the submission.

a) Is it an original NDA?

YES /_X__/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X__/

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

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:

_____

_____

Form OGD-011347 Revised 10/13/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

BOSENTAN HAS ORPHAN STATUS 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?

_____NO_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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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 /___/ NO /_X__/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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 /_X__/

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 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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 8.

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.

(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 8:

_____

(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:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 /___/

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

_____ _____

_____ _____

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 /___/

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

_____ _____

_____ _____

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"):

_____ _____

_____ _____

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: _____

_____

/S/

_____

Signature +Date
Title: Regulatory Health Project Manager

/S/

_____

Signature of Office/ Date 11-20-01
Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

FDA Links Searches Check Lists Tracking Links Calendars Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

View as Word Document

NDA Number:	021290	**Trade Name:**	BOSENTAN 62.5MG/125MG TABLETS
Supplement Number:	000	**Generic Name:**	BOSENTAN 62.5MG/125MG TABLETS
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	PULMONARY ARTERIAL HYPERTENSION
Action Date:	11/17/00		

Indication # 1 Pulmonary Arterial Hypertension
~~Label Adequacy: Other - See Comments~~
Formulation Needed: Other
Comments (if any): The pediatric requirement was waived because this drug has orphan status.

Ranges for This Indication

Lower Range	Upper Range	Status	Date
0 years	Adult	Waived	

Comments: Orphan status

This page was last edited on 8/30/01

/S/ 8/30/01
Date

Memo

Roche

Pharmaceuticals

To:	Whom it may concern	
Copies:		
From:	Mr. H. De Wilde	PDO, Bldg. 651
Date:	September 29, 2000	

Ref. Debarment Certification

To whom it may concern,

I, the undersigned, hereby certify that F. Hoffmann-La Roche did 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 H of the contract (see Appendix; item 301-323) , which were transferred to Actelion during the period of November and December 1998.

Henk de Wilde
Clinical Team Leader Bosentan

Isaac Kobrin, MD
Head of Clinical Development

ACTELION
Creative Science for Advanced Medicine

Allschwil, 23 October, 2000

To whom it may concern

I, the undersigned, hereby certify that Actelion Pharmaceuticals Ltd. did 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 of this document.

Isaac Kobrin, MD
Head of Clinical Development

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PATHEON

Patheon Inc.
Toronto Region Operations
2100 Syntex Court
Mississauga, Ontario, Canada L5N 7K9
Tel: (905) 821-4001 Fax: (905) 812-6789

June 23, 2000

Certification of Debarment
(FD&C Act 306 (k) (1))

Actelion Ltd.
Gewerbestrasse 18
CH-4123 Allschwil, Switzerland

Product : Bosentan film-coated tablets

We hereby certify that personnel at Patheon Inc. Toronto Regional Operations are screened and no Patheon employees are included in the current Debarment listing.

Jeff Derraugh
Manager, Group Compliance

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

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
THOMAS WIDMANN	SENIOR VICE PRESIDENT
FIRM/ORGANIZATION: ACTELION PHARMACEUTICALS Ltd.	
SIGNATURE	DATE: Nov. 6, 2000

Paperwork Reduction Act Statement

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Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

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DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Secondary Review

NDA: 21-290

Sponsor: Actelion Ltd.

Submission: Original NDA for the use of bosentan in the treatment of pulmonary hypertension.

Review date: July 11, 2001

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Summary: Bosentan is clearly effective in the treatment of pulmonary hypertension. Whether it should be approved for use in primary pulmonary hypertension, depends upon the value one places on a symptomatic benefit appreciable only in the aggregate population, compared with various risks, including some not discernible in a small population.

Distribution: NDA 21-290

HFD-110/Project Manager

HFD-110/Stockbridge

HFD-710/Lawrence

HFD-110/Gordon

HFD-110/Koerner

HFD-860/Robbie

This review is based upon primary reviews by Drs. Koerner (pharmacology), Robbie (biopharmaceutics), Gordon (medical), and Lawrence (statistical).

Bosentan is an endothelin receptor antagonist, with about 2-fold higher affinity for ET_A receptors than for ET_B. The effect of endothelin receptor antagonism is a reduction in systemic and pulmonary vascular resistance.

Animal toxicology testing was performed at high multiples of the proposed dose in man. Findings included hepatic enzyme elevations (reversible upon discontinuation), obstructive hepatotoxicity, anema (thought to be related to reduction in vascular permeability), testicular tubular atrophy, and oligospermia[1]. Bosentan was teratogenic and fetotoxic, findings shared with other endothelin receptor antagonists. Bosentan was not genotoxic. Final assessment of carcinogenicity is pending.

The proposed indication is for the treatment of primary pulmonary hypertension.

Bosentan is about 50% orally bioavailable; at the maximum recommended dose, food has no significant effect on bioavailability. Circulating bosentan is largely bound to albumin. Bosentan is extensively metabolized by CYP 3A4 and 2C9. One of the metabolites contributes an estimated 20% to the overall activity. Metabolites of bosentan appear mostly in bile. Use in patients with even mild hepatic impairment is contraindicated.

[1] *Testicular effects have been reported for other drugs with a similar mechanism of action.*

Bosentan is a significant inducer of CYP 3A4 and 2C9, resulting in predictable effects on its own metabolism (50% reduction in steady-state plasma levels) and that of other drugs.

Studies of pharmacokinetic interactions yielded results commensurate with the metabolism studies. Cyclosporine and ketoconazole significantly increased plasma levels of bosentan. Warfarin, simvastatin, and glyburide lowered plasma levels of bosentan. Digoxin, losartan, and nimodipine had no interactions with bosentan.

Most of what is known about pharmacokinetics of bosentan came from studies of normal volunteers. Subjects with PPH had a clearance of 3.8 L/h, compared with 9 L/h in normal subjects.

The sponsor performed two studies to demonstrate clinical benefit to treatment of pulmonary arterial hypertension. Subjects could have pulmonary hypertension of ~~unknown etiology (about 2/3 of subjects) or secondary to connective tissue or~~ autoimmune diseases. They were WHO class III-IV, treated with vasodilators, diuretics, digitalis, or anticoagulants, as needed. Moderate elevations in hepatic enzymes or anemia were exclusions. Both studies evaluated 6-minute walking distance as the primary end point and a variety of symptom, functional status, and outcome variables as secondary end points. Both trials were parallel and placebo controlled. The first (Study 351) enrolled 32 subjects and randomized 2:1 to bosentan 125 mg bid or placebo, and the other (Study 352) randomized 213 subjects 1:1:1 to bosentan 125 or 250 mg bid or to placebo. The duration of randomized treatment was 12 (Study 351) or 16 weeks (Study 352); subjects randomized to bosentan received 62.5 mg bid for the first 4 weeks.

There were few deaths or other reasons for discontinuation from these studies, so the analyses are fairly insensitive to how such subjects are handled, and treatment groups were reasonably well matched for demographic and baseline characteristics. Both trials met prespecified statistical criteria for deciding the trials found something on their primaries. Qualitatively, the two trials showed much the same result on the primary end point. The placebo group, on average, improved a few meters at 4 weeks and was a few meters less than baseline at study end, while the active treatment groups showed improvements by week 4 that were at least sustained to the full period of follow-up. Subjects in Study 352 continued on blinded treatment out to 28 weeks. The change in walking distance was about 20% on 125 mg bid in Study 351 and 11% (125 mg bid) and 16% (250 mg bid) in Study 352. The largest changes in walking distance were seen in subjects with lower baseline walking distances.

Dr. Robbie has performed NONMEM analysis of 6-minute walk data from studies 351 and 352. This analysis is reproduced in the figure below.

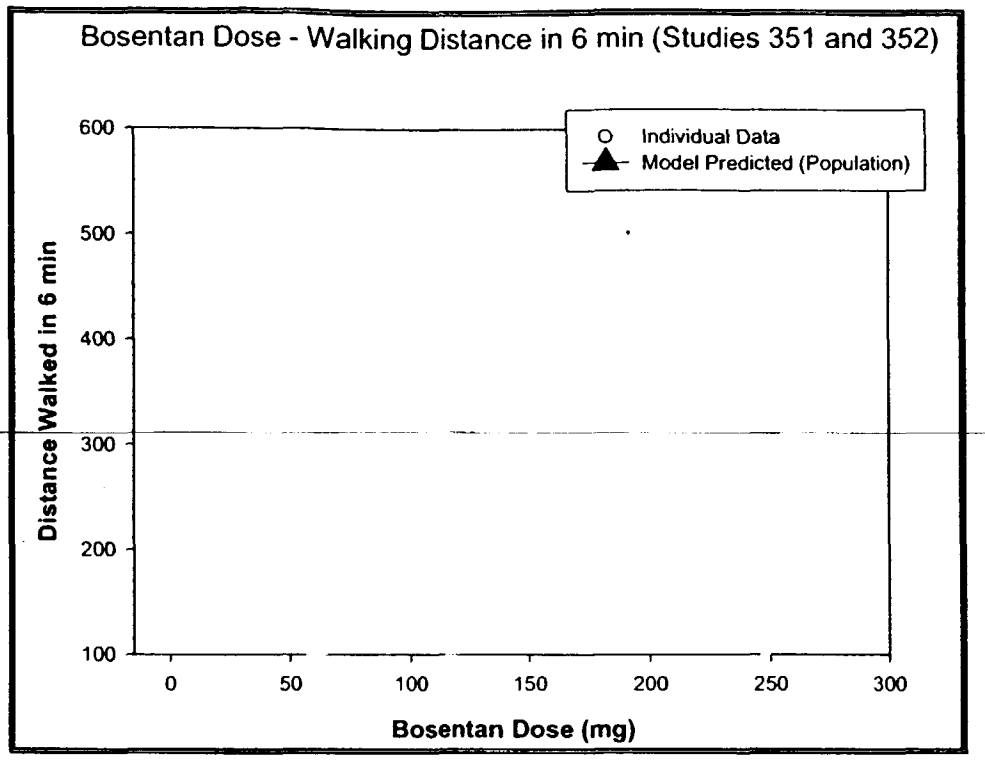

Figure 1. Analysis of dose-response

Two points can be made from this figure. One is that very little difference can be expected from doses of 125 and 250 mg[2]. The second is that the effect of treatment with bosentan, while unequivocal in a large population, will not be discernible in an individual patient.

Unlike the overall analysis, an analysis of walking distance by category of etiology is sensitive to the mode of handling early withdrawals, because 4 of the 5 subjects assigned a zero post-baseline walking distance came from the cohort with scleroderma. With these values included, this group has less of a treatment effect, but with them excluded from the analysis, there appears to be no effect of etiology.

Although there are no studies permitting titration during long-term treatment, tolerance or loss of effectiveness did not appear to be problems out to 28 weeks of placebo-controlled experience.

Supporting data came from the analyses of time to clinical worsening, which tended to be longer on bosentan, Borg dyspnea index, where the score rose (greater perceived exertion) on placebo and declined on bosentan, WHO functional class assessments, where improvement was more likely on bosentan than on placebo, and a trend for less need for additional therapy on bosentan.

Bosentan use was associated with reduction in blood pressure, -10.8/-8.6 mmHg in Study 351 and a smaller but directional similar change in Study 352. There is no

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[2] *Dr. Robbie modeled these data including or excluding subjects assigned a zero walking distance, assuming a normal or log-normal distribution, and with a linear or Emax model. Inclusion of subjects with a zero walking distance is a conservative approach to deciding if there is a treatment effect, but it inappropriate for estimating the magnitude of effect. The fits using a log-normal distribution were about 1% better than those with the normal distribution. After adjustment for the larger number of free parameters, the Emax model was about 20% better than the linear model. In general, this analysis confirms that the 250-mg dose is little better from the 125-mg dose.*

clinically significant effect on heart rate in either study. However, at doses up to 2000 mg/day, bosentan was scarcely distinguishable from placebo in effects on blood pressure in studies of essential hypertension.

Baseline and on-treatment invasive hemodynamic assessments are available for Study 351. The changes from baseline and placebo were PAP -6.7 mmHg, PVR -414, CI -1.0 L/min/m^2, RAP -6.2 mmHg, and PCWP -3.8 mmHg, all nominally statistically significant. These changes are consistent with the posited mechanism of action.

The safety database for bosentan is derived from about 250 subjects in controlled studies of pulmonary arterial hypertension and about 750 subjects in controlled trials for other indications, mostly chronic heart failure. The mean dose in the controlled studies overall was >1000 mg/day, but the maximum in studies of pulmonary hypertension was 250 mg bid. The mean duration was about 4 weeks in controlled studies generally, but it was more than 12 weeks in pulmonary hypertension.

Rates of withdrawal were similar in placebo and active treatment groups of all controlled studies, with the most common reasons for withdrawal being "sponsor's decision" (24%), adverse events (11%), and death (4%).

Worsening pulmonary hypertension was the attributed cause of death in the few deaths among bosentan subjects in pulmonary hypertension studies.

Serious adverse events have been reported in 8% of bosentan subjects in studies of pulmonary arterial hypertension. The most common adverse event associated with withdrawal was hepatic enzyme elevation, much more common on bosentan than on placebo. The database is simply too small to detect or exclude many other events that may be treatment related.

Elevations in AST or ALT to at least 3 times upper limit of normal occurred in about 10% of all subjects receiving bosentan; of these, about 1/3 had elevations to greater than 8 times upper limit of normal. Elevations in gamma GT were about as common, while elevations in bilirubin or alkaline phosphatase were much less common. An analysis the sponsor performed is suggestive that elevations in hepatic enzymes are weakly dose-related and infrequent in the first few weeks of treatment.

Individual case histories for hepatic enzyme elevations are described in Dr. Gordon's review. There are cases of positive rechallenge. In most cases, enzyme levels normalized when the study drug was terminated, although it is difficult to specify the time course for recovery. Liver enzyme elevations were sometimes accompanied by fever and abdominal pain.

The only other laboratory abnormalities with any likely relationship to bosentan were hematologic. About 5% of bosentan subjects had anemia as an adverse event, and about twice as many subjects had clinically significant reductions in hematocrit or hemoglobin. The drop in hemoglobin appears soon after exposure to bosentan, and it averaged about 1 g/dL with long-term exposure. One subject underwent bone marrow assessment which showed a normocellular marrow with adequate hematopoietic reserves. Some subjects were treated with packed red cells. Anemia was not associated with identified sites of hemorrhage.

Heart rate and ECG intervals were not significantly affected by bosentan.

Should bosentan be approved for the treatment of pulmonary arterial hypertension?

To its credit, bosentan was shown to be effective in improving walking distance in two prospective studies, for which walking distance was the primary end point. The magnitude of effect on walking distance was probably clinically meaningful, and it was accompanied by positive trends in other measures of symptomatic benefit.

On the other hand, symptomatic benefit is not an improvement in outcome. No trends with respect to outcome, positive or negative, can be discerned from the available data. Furthermore, inter- and intra-subject variability is large compared with the mean treatment effect, so physicians and patients will generally not be sure that changes in symptoms are attributable to treatment.

The improvement in symptoms carries with it numerous risks. They include teratogenicity, P450 enzyme interactions affecting concomitant medications, hepatotoxocity, and anemia. Although these risks did not result in clearly worsened outcome, it is difficult to draw much comfort given the small size of the safety database and the likely less aggressive monitoring that occurs in clinical practice.

The population studied with bosentan included primary pulmonary hypertension and . The standards for approval should probably not be the same in these areas. Flolan (epoprostinol) is only indicated for treatment of primary pulmonary hypertension, where its considerable risks, primary related to mode of administration, do not overshadow a mortality benefit. One should consider whether bosentan delays the initiation of Flolan, and, if so, whether that is a good idea. There is no approved treatment for secondary pulmonary hypertension, so symptomatic improvement is clearly worth some risk.

Clearly, a case can be made for approval. Bosentan is effective in improving the exercise capacity in patients with pulmonary hypertension of various etiologies. This benefit was manifest in other indices of symptomatic improvement. The drug will need close monitoring, but irreversible harm can probably be prevented by appropriate surveillance.

A reasonable case can also be made against approval, particularly in primary pulmonary hypertension. Patients who receive the drug will never know whether their own symptoms are improved because of it, or how much worse they would feel off of it. They will incur real risks—from inadequate attention on the part of physicians to hepatic and hematologic effects or to drug interactions and from inadequate exploration of safety in the target population—for no certain gain. In terms of outcome—mortality or disease progression, the data say there is no benefit, but there may be irreversible harm in delaying the initiation of life-prolonging treatment.

Project Manager Overview of NDA 21-290
Tracleer (bosentan) 62.5 & 125 mg Tablets
August 31, 2001
Revised September 5, 2001
Revised November 9, 2001

Background:
Bosentan, an endothelin receptor antagonist, is currently under development for pulmonary arterial hypertension (IND) and (IND). The Division of Orphan Drug Products designated bosentan an orphan drug (Ref# 00-1342) for the treatment of pulmonary arterial hypertension on October 6, 2000. The Chemistry, Manufacturing and Controls, and the Nonclinical Pharmacology and Toxicology sections of this NDA were presubmitted on September 25, 2000. Tracleer (bosentan) has not been approved for sale in any country.

An End-of-Phase 2 meeting was held on March 18, 1998. The Chemistry Pre-NDA meeting was held on March 31, 2000, and the Clinical and Non-Clinical Pre-NDA meeting was held on June 6, 2000.

Actelion is seeking the following indication for bosentan: Pulmonary arterial hypertension.

Medical Reviews
Dr. Gordon wrote separate reviews for safety and efficacy. The Efficacy review is dated June 29, 2001 and the Safety review is dated July 6, 2001. In her Medical Review of Safety and Efficacy – Conclusions dated July 6, 2001, Dr. Gordon stated the following:

Bosentan should be approved for improving walking distance in patients with WHO functional class III or IV, who are not responding adequately to conventional therapy, and are not taking Flolan. Because of the toxic effects on the liver and the serious drug-drug interactions, its recommended that a patient registry with education for physicians who treat patients with PAH be implemented prior to the marketing of bosentan.

Dr. Gordon had no labeling recommendations in her review.

Statistical Reviews
Clincal
There are two statistical reviews. The first review, dated March 23, 2001, evaluates the first, smaller, study of 32 patients and awaits submission of the second major study that was subsequently submitted May 1, 2001.

In his second review dated June 6, 2001, Dr. Lawrence stated that the two placebo controlled studies showed persuasive evidence that 12 to 16 weeks of treatment of bosentan increases the change in walking distance relative to placebo. The incidence of abnormal hepatic function and flushing appeared to be greater in the bosentan groups in both studies. No other treatment related adverse events appeared to be associated with the use of bosentan 125 mg or 250 mg b.i.d. for 12 to 16 weeks.

Carcinogenicity
In her reviews dated August 29, 2001, Dr. Kelly made numerous observations of the mouse and rat carcinogenicity studies. She made no labeling recommendations.

Biopharmaceutics
In his review dated July 13, 2001, Dr. Robbie stated that the Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-290 and finds the clinical pharmacology and biopharmaceutics section acceptable provided labeling comments #1-10 are addressed. See review page 14.
He also sates that the sponsor is requested to change the proposed dissolution medium from 1% sodium lauryl sulfate in water tc sodium lauryl sulfate in water with a dissolution specification of Q not less than % in 30 minutes.
In his review dated November 1, 2001, Dr. Robbie stated that, based on the new information provided by the sponsor, the proposed dissolution specification for bosentan should be Q not less than % dissolved in 30 minutes in 1% sodium lauryl sulfate in water at 50 rpm.k This will be added to the approval letter.

Pharmacology
In his review dated August 30, 2001, Dr. Koerner stated that bosentan is recommended for approval of the treatment of pulmonary arterial hypertension from a pharmacology perspective, despite the toxicities he mentioned in his review, because of the seriousness of the proposed indication and the lack of alternative oral therapy. Labeling considerations are enumerated on pages 158 and 159 of Dr. Koerner's review.

Chemistry
In his second chemistry review dated September 4, 2001, Dr. Uppoor states that, from the CMC point of view, the application is recommended for approval. The OCPB review team's outstanding recommendations should be communicated to the applicant. Validation of the analytical methods at FDA laboratories is pending at this time and the applicant's continued cooperation to satisfactorily complete such method validation should be requested.

Trade Name Review: In their final trade name review dated August 20, 2001, OPDRA found the proprietary name, Tracleer, acceptable.

EER: The overall EER recommendation, dated July 19, 2001, was ACCEPTABLE.

Categorical exclusion for environmental assessment is acceptable, See page 80 of Chemistry Review #1.

The sponsor plans to the bottles for shipment, therefore, there is no carton labeling. They have submitted shipping labels.

Advisory Committee Meeting
An advisory committee meeting was held on August 10, 2001. The Committee unanimously recommended that bosentan be approved for the treatment of pulmonary hypertension. Six members recommended labeling for dosing regimens as administered in the clinical trials. Three members recommended starting with a 62.5 mg dose twice per day and assessing symptoms at 4 weeks before dose-escalation. The Committee recommended that patients should be enrolled in a registry to obtain additional information about the safety of bosentan. Long-term monitoring, especially for liver toxicity, was also recommended. Female patients should have a pregnancy test prior to administration of drug and avoid becoming pregnant while taking bosentan. In addition, bosentan should carry a black boxed-warning regarding its potential teratogenic effects.

RPM Review of Final Printed Labeling

I have reviewed the electronic final printed labeling (package insert) and medication guide that were submitted by the sponsor on November 2, 2001. The labeling is in accordance with the draft labeling that accompanied the approvable letter and the agreed upon labeling changes that were discussed in the October 31, 2001 teleconference with the sponsor.

RPM Summary

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

S

Zelda McDonald, RPM

Teleconference Minutes

Telecon Date:	October 31, 2001
Date Requested:	October 29, 2001
NDA:	21-290
Drug:	Tracleer (bosentan) Tablets
Sponsor:	Actelion
Type:	Labeling
Classification:	C
Telecon Chair:	Robert Temple, M.D.
Telecon Recorder:	Zelda McDonald
~~External Participant Lead:~~	~~Thomas Lategan, Ph.D.~~

FDA:

Robert Temple, M.D.	Director, Office of Drug Evaluation I, HFD-101
DouglasThrockmorton, M.D.	Deputy Director, HFD-110
Norman Stockbridge, M.D, Ph.D.	Team Leader, Medical, HFD-110
Zelda McDonald	RHPM, HFD-110

Actelion Inc:

Tom Lategan, Ph.D.	VP, US Regulatory Affairs
Peter Herrmann, PharmD.	Global Head of Regulatory Affairs (Switzerland)
Simon Buckingham, DVM, Ph.D.	President, Actelion US
Isaac Kobrin, M.D.	Clinical Research, (Switzerland)
Sebastien Roux, M.D.	Clinical (Switzerland)
Richard Rylander	Sales Operations
Rob Etherington	Marketing US

Background

Bosentan is currently under development in pulmonary arterial hypertension (IND Actelion applied for and received orphan drug status for bosentan for pulmonary arterial hypertension. Actelion has submitted an NDA seeking approval of bosentan for the treatment of pulmonary arterial hypertension and an approvable letter issued on September 17, 2001. The Division had e-mailed marked-up labeling and a marked-up medication guide to Actelion on October 26, 2001. On October 29, 2001 Actelion e-mailed a package insert that incorporated the changes made by the Division. The purpose of this teleconference was to have a final discussion and reach agreement about the package insert, medication guide and any other issues pertaining to the approval of the application.

Telecon:

The Agency went over changes that it had made to the October 29, 2001 submission, noting several editorial changes and the addition of the statement, "Monthly pregnancy test should be obtained." that was added to the end of the CONTRAINDICATION/Pregnancy section of the Black Box. Actelion agreed with the requested changes. This labeling could not be attached to these minutes because it was not provided in WORD and therefore could not be edited.

The Agency and Actelion agreed on several changes to the Medication Guide (see attachment).

The Agency agreed that if Actelion makes the agreed upon changes, they can submit final printed labeling.

The Agency stated that there were several other issues to consider:

1.

Actelion stated that they would examine it as well and see if they could come up with some alternative language.

2. Actelion agreed to do a phase 4 study to assess the effect of bosentan on sperm counts.

3. The Agency stated that Actelion would need to determine whether bosentan inhibits the effect of oral contraceptives. The Agency stated that Actelion should assess patients currently on bosentan and oral contraceptives to get preliminary answers. In addition, Actelion would need to submit a proposed protocol for further study of this issue.

   Actelion stated that they had not done such a study because they believed bosentan was such a mild enzyme inducer that the effects would be small. There were so many contraceptives, they wondered how one could be selected that would be representative of all of them. They did not think that there were many, if any, of their patients on oral contraceptives.

   The Agency suggested Actelion should study an estrogen based contraceptive and look at the ovulation rate. The Agency believed that there must be at least a few patients on oral contraceptives. The Agency asked Actelion to provide an idea as to what their proposal would be soon.

   Actelion committed to investigating further and coming back with a proposal.

4. Actelion asked when they could expect an approval letter. The Agency hoped to have resolution on the issues quickly and an action within a week or so.

- The Agency asked if Actelion would be using their "Know Your Medicine" brochure and when it would be given to the patient. The Agency was concerned that it may cause some confusion with the Medication Guide.

  Actelion stated that the "Know Your Medicine" brochure would be part of the physician's packet. The patient would receive the "Know Your Medicine" brochure when first diagnosed. Thereafter, the patient would be receiving only the medication Guide. The patient would receive the "Know Your Medicine" brochure only from the learned intermediary. Actelion asked if the "Know Your Medicine" brochure should be attached to the Medication Guide.

  The Agency stated that Actelion should consult with the Division of Drug Marketing Advertising and Communication on that question.

- The Division asked if Actelion had thought about making an instructional video for the patient.

  Actelion stated they have no firm plan at the moment.

- The Division asked what Actelion knew about liver toxicity

  Actelion stated that there was no new information other than what they had already told us. Once the study is they will submit all the data.

Signature minutes preparer: /S/ 11/14/01

Concurrence, Chair: /S/

Drafted: 11/2/01 Finaled: 11/14/01
RD:
Temple 11/9/01
Throckmorton 11/5/01
Stockbridge 11/2/01

Minutes of a meeting

Date of meeting:	September 27, 2001
Application:	NDA 21-290
Product:	Tracleer (bosentan)
Sponsor:	Actelion
Purpose:	to discuss proposed labeling and sponsor's proposed post-approval risk management programs
Participants:	
FDA	
Douglas Throckmorton, M.D.	Deputy Director, Division of Cardio-Renal Drug Products (HFD-110)
Norman Stockbridge, M.D., Ph.D.	Team Leader, Medical, HFD-110
John Koerner, Ph.D.	Pharmacologist, HFD-110
Gabriel Robbie, Ph.D.	Clinical Pharmacologist and Biopharmaceutist, Division of Pharmaceutical Evaluation I (HFD-860)
Cindy Kortepeter, Pharm.D.	Safety Evaluator, Division of Drug Risk Evaluation I (HFD-430)
Susan Lu, R.Ph.	Team Leader, Safety Evaluation, HFD-430
Rajendra Uppoor, Ph.D., R. Ph.	Chemist, Division of New Drug Chemistry I (HFD-810)
Colleen LoCicero	Regulatory Health Project Manager, HFD-110
Actelion	
Tom Lategan	Vice President, Regulatory Affairs
Simon Buckingham	President, Actelion US
Isaac Kobrin (via telephone)	Head, Clinical Research
Maurizio Rainisio (via telephone)	Biometry
Dick Rylander (via telephone)	Sales Operations
Martine Clozel (via telephone)	Head, Preclinical

Background

This meeting was scheduled following the issuance of the Agency's September 17, 2001 approvable letter for this new drug application. The purpose of the meeting was to discuss the sponsor's September 20, 2001 submitted proposed labeling and risk management program.

The meeting

Dr. Throckmorton started the discussion by noting that because the pre-meeting had lasted longer than expected, Dr. Temple would not participate in the meeting, as he had a previous commitment. He indicated, however, that the labeling was discussed in its entirety, along with the proposed risk management programs, in the pre-meeting with Dr. Temple and that Dr. Temple's comments and recommendations on both would be presented in this discussion.

Discussion Point #1: Tracleer Access Program (TAP)

The Agency requested clarification of the proposed closed distribution system (TAP) for Tracleer.

a

PRE DECISIONAL

The Agency needs to discuss further internally the adequacy of the proposed distribution system.

Discussion Point #2: Med Guide

The sponsor needs to rewrite their "Know Your Medicine" document as a Med Guide. Regardless of whether this is considered a formal Med Guide, the Med Guide format, as specified in 21 CFR Part 208, will need to be used. Additionally, the Tracleer package insert will need to include a "patient information" section. This section can be brief and reference the Med Guide. The sponsor should contact Dr. Haffner in DDMAC to discuss the details of the Med Guide, as he had some recommendations on this.

Discussion Point#3: Labeling

The remainder of the meeting discussion was devoted to the labeling. See attached marked-up labeling.

Conclusion

The sponsor committed to revise the package insert labeling, based upon the meeting discussion, and submit the revised labeling to the Agency within the next several days. It is likely that a teleconference the week of October 1-5 will be needed to further discuss the labeling. Dr. Lategan will be in contact with the Agency to schedule this. The sponsor agreed also to revise and reformat their "Know Your Medicine" document to fit the content and format of a Med Guide, as described under 21 CFR Part 208. The Agency will need to discuss further internally the proposed risk management program, including the closed distribution system and Med Guide.

/S/

Signature, Meeting Recorder:_____Colleen LoCicero

Concurrence, Meeting Chair:_____/S/_____Douglas Throckmorton, M.D.

drafted: 10/1/01 finaled: 10/4/01

rd:
Uppoor/10/2/01
Robbie/10/2/01
Koerner/10/3/01

Stockbridge/10/3/01
Throckmorton/10/3/01
Kortepeter/10/3/01
Lu/10/3/01

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

NDA #21,290

Memo to File: Teleconference with Actelion

Teleconference Date: January 11, 2001

Teleconference Participants

Sponsor
Tom Lategan, V.P., Regulatory Affairs, Actelion
Martine Clozel, Head of Preclinical Development, Actelion
Peter Herrmann, Head of Regulatory Affairs, Actelion
Marc Aellen, Biometry, Actelion

FDA
John Koerner, Ph.D., HFD-110
Roswitha Kelly, M.S., HFD-710

Re: NDA 21290
Amendment Date: December 20, 2000

Background: Actelion resubmitted electronic datasets (Submission dated December 20, 2000) for rat and mouse carcinogenicity studies since the initial datasets submitted were not analyzable by SAS and did not conform to FDA's January 1999 guidance on electronic datasets. However, the resubmitted datasets are also not analyzable by SAS, and also do not conform to the FDA's January 1999 guidance on electronic datasets.

Purpose of Teleconference: To resolve the format problems with the electronic datasets for the rat and mouse carcinogenicity studies.

Action Items

1. The sponsor will resubmit the electronic datasets as SAS datasets per the January 1999 agency guidance on electronic submissions. The sponsor will provide these SAS datasets to the agency by January 19, 2001.

2. The two files (header and data files) previously submitted for each carcinogenicity study will be merged. Hence, only one file will be submitted for the mouse study, and one file will be submitted for the rat study.

3. The sponsor can contact Ted Guo at (301) 827-3109 if they need assistance.

CC:
Original NDA
HFD-110
HFD-110/ZMcDonald
HFD-110/CResnick
HFD-110/JKoerner
HFD-710/RKelly
HFD-715/TGuo