CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-290

Correspondence

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-290

INFORMATION REQUEST LETTER

8/13/01

Actelion Limited
Attention: Thomas Lategan, Ph.D.
Vice President, Regulatory Affairs
56 Huckleberry Lane
North Andover, MA 01845

Dear Dr. Lategan:

Please refer to your 11/17/2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRACLEER (bosentan tablets) tablets, 62.5 mg and 125 mg.

We also refer to your submissions dated 9/25/2000, 10/11/2000, 3/5/2001, 5/31/2001, 7/26/2001, and 8/6/2001.

We are reviewing the Chemistry,manufacturing and controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

DRUG SUBSTANCE RELATED

1. A of bosentan in the in pH 2.5 aqueous phosphate buffer used for assay (see volume 1.1, page 175,), and in % or 1% aqueous solution of sodium lauryl sulfate (used as a dissolution medium) are requested.

2. Methods for the analysis of the following reagents should be stated:

   Also, minimum acceptance criterion for the assay of should be indicated.

3. Use of alternate procedure(s) is acceptable, if information about the actual use of those procedures [as in items (a.) to (d.) below] is provided in the application, and it is shown that, use of the alternate procedure yields equivalent end-product material with respect to assay and impurity profile.

(a) It is noted that have been quoted as alternate solvents for use in of the synthesis (see pages 69 and 103). Information on the actual use of these solvents should be provided to the application.

(b) Details of alternative procedure (see page 69) regarding should be provided in the application. If is isolated and characterized, its specification should be submitted to the application.

(c) Please state whether you have used (see pages 70 and 103) in the synthesis.

4. It is noted that you have proposed to use in the future. In this context, you are suggested to follow the guidance provided in "Guidance to the Industry, BACPAC I: Intermediates in Drug Substance Synthesis; Bulk Actives Postapproval Changes: Chemistry, Manufacturing and Controls Documentation" while adding a new supplier of an intermediate or redefining an intermediate as a starting material.

5. The percent yield (or its range, as may be applicable) for each of the intermediates or in-process intermediate mixtures obtained during the synthesis of bosentan monohydrate should be provided to the application.

6. Test procedures for the quantitative analyses of mixture at the synthesis should be submitted to the application. If is tested using the procedure stated on pages 81 and 82, it should be stated so in the application.

7. The following items (a.) to (d.) should be clarified:

a. Chemical structure of related substance Ro 47-0005/001 (stated on pages 111 and 112), as a single impurity or as two separate impurities.

b. Chemical structure for related substance Ro 64-4350 (see page 105); or it is an erroneous reporting in place of impurity Ro 62-4350 (see pages 115, 133, impurity 9).

8. Please indicate the holding time established, with justification, for between its manufacturing and its use in the drug substance synthesis. Also, the holding time(s) established for storing each of the intermediates during the synthesis, in between , and especially at the should be submitted to the application.

9. The acceptance criteria for total impurities should be revised to state, (see volume 1.1, page 170).

10. Information on the use of reference standards, or other suitable particle size reference standards used for calibrating the should be provided to the application.

11. Please justify with data, that Ro 47-9931 would not interfere in the stability analysis of bosentan monohydrate drug substance [as well as in the analysis of related substances in bosentan film coated tablets (see volume 1.4, pages 192-197, 203-208, 357)].

12. Please clarify that impurities identified on page 136 of the application are formed at

13. Procedure(s) used for the analysis of in bosentan monohydrate should be submitted to the application. It is suggested that the actual content in ppm of the above residual solvents in the three representative batches should be provided to the application. Upon review of such data, your proposal to bosentan monohydrate will be reevaluated.

14. It is noted that exposure of drug substance to quantitative terms such as Current information provided in the application should be amended to include quantitative data.

15. Based on up to of stability data submitted in the application upon storage of drug substance at 25°C/60% RH (relative humidity) and 30°C/75% RH, a re-test date of two years will be acceptable. Re-test period for drug substance is acceptable only to the extent of satisfactory long term data submitted in the application.

16. Based on real time data submitted in the application, controlled room temperature conditions of up to 30°C and 75% RH should be recommended for storing the bulk drug containers of Bosentan Micropowder (see page 263).

DRUG PRODUCTS RELATED (for both 62.5 mg and 125 mg strengths)

17. It should be clarified in the application that components (such as magnesium stearate, glyceryl behenate) that will be used in the drug products will not be procured from

18. Regulatory acceptance criteria proposed for the contents of Ro 47-0005, and unidentified impurities in bosentan drug substance (see page 170, volume 1.1) are respectively. On pages 2 and 3 of volume 1.2, they are recorded as respectively. The acceptance criteria for Ro 47-0005, and unidentified impurities in bosentan drug substance should be revised in the master batch record. Also, the acceptance criteria stated for of 1% m/v bosentan solution in should match with the proposed regulatory acceptance criteria.

19. Chemistry, manufacturing and controls information for and should be provided to the application. If such information can be found in a DMF, a

letter of authorization from the DMF holder to refer to their current DMF pages containing such information should be submitted to the application.

20. ' by using a mentioned on page 355 (box 4 from above) can only be included if three consecutive drug product validation batches each will be manufactured, ' and ' , and the resulting drug product batches are shown to be identical. Otherwise, the proposed should be removed from the flow chart of the manufacturing process.

21. Master batch records should be revised to include the use of which will emboss 62,5 and 125 identification markings respectively on tablets of the two strengths.

22. Results of particle size analysis performed on prior to their for registration batches should be provided to the application.

23. Process control ranges for in-process tests for tablets after "tablet compression" and "after film coating" should be included in the batch records for both 62.5 mg and 125 mg tablets.

24. Results of total unidentified, unspecified degradants in the drug product should be included in the application.

25. Information about the identification markings 62,5 and 125 respectively that will be present on the tablets should be included in the regulatory specification under appearance.

26. Collection of stability sample(s) should occur on the scheduled due dates. However, if deviations occur, they should be justified. Therefore, the proposal to collect stability samples the scheduled due date should be revised.

27. Based on stability data submitted in the application at this time on three primary (registration) batches, and no statistical evaluation on the data, an expiry date of can be recommended at this time. Additional shelf life can be recommended based on evaluation of real time, long-term stability data that may be submitted in the future. If results of two-sided regression analysis (using 95% confidence interval) on available stability data of supportive and primary batches will be provided, then, results of those statistical analysis will be evaluated as justification in support of the proposed expiration dating period of .

28. Based on data provided to date, it is recommended that the acceptance criteria for total unspecified, unidentified degradation products (should be reduced from the currently proposed acceptance criteria of maximum %. Actual data should be taken into consideration for setting the reduced acceptance criteria.

29. It is noted that individual unspecified and unidentified degradants for the drug products are not reported in the stability data submitted application, as proposed on pages 74 and 75 of

Volume 1.5. It is recommended that both individual, and total unspecified and unidentified drug product degradants should be reported in the study results.

30. Current regulations do not allow for : stability testing of drug products. Therefore it is recommended that at least one batch per year of each packaging configuration of drug product (or as manufactured, if less often than one batch per year) should be entered into ongoing stability program.

31. Whenever post-approval changes are made in the manufacturing process, or in the container closure system of an approved drug product as proposed on pages 111 and 112 of volume 1.4, then, such changes should be reported to the Agency according to applicable 21 CFR regulations, and/or as recommended in CDER Guidance to Industry: Changes to an Approved NDA or ANDA, or in CDER Guidance to Industry: Scale Up and Post Approval Changes – Immediate Release Drug Products, or according to Section 506A of the Federal Food, Drug and Cosmetic Act, as amended, or according to Section 116 of the Food and Drug Administration Modernization Act, 1997.

32. It is recommended that a minimum of four testing points should be retained for reporting stability results for all batches of drug products up to and including their actual shelf life.

33. It should be clarified in the application whether ' ' or, any or ' will be used in the stability studies of production scale and annual batches of drug products.

34. It is observed that the weight of placebo tablets that were used in investigational clinical studies was higher by approximately % (see page 198 of Volume 1.5) for the 62.5 mg tablets, and % (see page 199 of Volume 1.5) for the 125 mg tablets. A justification is requested for the difference in the weights of placebo tablets and the drug substance containing tablets that were used in investigational clinical studies.

35. Please clarify whether the number of drug substance batch 707004 stated to be used for the manufacturing of drug product batch PT 2241 T52 used in Phase 3 clinical studies is accurate.

36. A coefficient of correlation for the linearity of area count versus % concentration in solution being analyzed should be provided to the application (see pages 234 to 237, volume 1.1). Also, the stated in item 4.3. and in item 4.2. (on page 234) do not appear to be correct. Corrected information should be provided to the application.

37. The Directions for Testing, sections 5 and 6, for both 62.5 mg tablets (pages 190 to 200, volume 1.4) and 125 mg tablets (pages 201 to 211) do not provide for the testing of related substances and unidentified impurities. The time of minutes is insufficient to elute and quantitate the three potential impurities (see pages 357, 366, volume 1.4) that can be present in the drug product. Those sections should be revised in the application.

38. The alternate method for the identification of bosentan in bosentan film coated tablets by part of tablet (see page 213, volume 1.4) and its validation data should be submitted to the application, when it will be used for testing of drug product(s) for commercial distribution.

39. Labels that will be used on in-process bulk containers of drug products should be submitted to the application.

40. It should be clarified in the application whether you intend to manufacture "Physician's Sample" pack size(s) of drug products.

41. The following comments apply to the proposed drug product labels of both 62.5 mg and 125 mg tablets (and items 41 to 42 may be revisited again at a later date):

a. Bottle labels should indicate the number of tablets in the container.

b. Currently stated wordings should be revised to read bosentan tablets.

c. An asterisk should be placed after 62.5 and 125 on the label, such as 62.5* and 125*.

d. On the label of TRACLEER™ 62.5 mg tablets, on the side panel it should state: * Each tablet contains 64.541 mg of bosentan, equivalent to 62.5 mg of anhydrous bosentan.

e. On the label of TRACLEER™ 125 mg tablets, on the side panel it should state: * Each tablet contains 129.082 mg of bosentan, equivalent to 125 mg of anhydrous bosentan.

f. The currently stated storage temperature of should be revised to read, Store at 20° - 25°C (68° - 77°F) [see USP Controlled Room Temperature].

g. Mock up bottle labels that will be used on both 40 cc bottles and 60 cc bottles, and for both 62.5 mg and 180 mg strength tablets should be submitted to the application.

42. The following revisions apply to the **DESCRIPTION** section of the proposed package insert:

Revised sentence:

DRAFT

43. The following revisions apply to the **HOW SUPPLIED** section of the proposed package insert (see volume 1.2, page 147):

Current sentences:

Revised sentences:

62.5 mg film coated, round, biconvex, orange-white tablets, embossed with identification marking 62.5, packaged in a white high density polyethylene bottle and a white polypropylene child resistant cap.

NDC XXXXX-XXXX-XX: Bottle containing 60 tablets.
NDC XXXXX-XXXX-XX: Bottle containing 180 tablets.

125 mg film coated, oval, biconvex, orange-white tablets, embossed with identification marking 125, packaged in a white high density polyethylene bottle and a white polypropylene child resistant cap.

NDC XXXXX-XXXX-XX: Bottle containing 60 tablets.
NDC XXXXX-XXXX-XX: Bottle containing 180 tablets.

Add this sentence: Rx only.

44. The following revisions apply to the **STORAGE** (see page 147) section of the proposed package insert:

Current sentence:

Revised sentence: Store at 20 - 25°C (68 - 77°F) [see USP Controlled Room Temperature].

CMC/BIOPHARMACEUTICS REVIEW COMMENTS

1. The proposed concentration of 1% w/v sodium lauryl sulfate is considered to be high. Similar dissolution performance is obtained with w/v sodium lauryl sulfate in water.

2. We recommend the following dissolution method, medium and specification; dissolution not less than ( )% (Q) dissolved in 30 minutes in odium lauryl sulfate in water using USP apparatus II (paddle) at a speed of 50 rpm.

If you have any questions, call Zelda McDonald, Consumer Safety Officer, at 301-594-5333.

Sincerely,

8|13|01

{See appended electronic signature page}

/S/

Kasturi Srinivasachar, Ph.D.
Chemistry Team Leader, DNDC I for the
Division of Cardio-Renal Drug Products, HFD-150
DNDC 1, Office of New Drug Chemistry
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-290

INFORMATION REQUEST LETTER

Actelion Ltd.
Attention: Isaac Kobrin, M.D.
Gewerbestrasse 16
Allschwill
CH-4123
Switzerland

Dear Dr. Kobrin,:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tracleer (bosentan) Tablets.

We are reviewing the clinical section of your submission and request that you send us the database for laboratory values and all adverse events in SAS readable form. Also, please include a marked-up case report form so we will know what codes were used.

We need your prompt written response to continue our evaluation of your NDA.

If you have any questions, please call:

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

Sincerely,

3/22/01

/S/

{See appended electronic signature page}

Raymond J. Lipicky, M.D.
Divsion Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-290

Actelion Ltd
Attention: Anne Cathrine Sund, M.D.
Gewerbestrasse 16
Allschwill
CH-4123
Switzerland

Dear Dr. Sund:

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

Name of Drug Product: Tracleer (bosentan) 62.5 mg and 125 mg Tablets

Review Priority Classification: Standard (S)

Date of Application: November 17, 2000

Date of Receipt: November 17, 2000

Our Reference Number: NDA 21-290

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 16, 2001 in accordance with 21 CFR 314.101(a).

We note that you have been granted orphan status, therefore, pediatric data are not required.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA 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: Division Document Room
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: Division Document Room
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, please call:

1/11/01

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

Sincerely,

1/12/01

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

October 6, 2000

Dear

Reference is made to the orphan-drug application received March 17, 2000, submitted on behalf of Actelion Life Sciences Ltd. pursuant to Section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb) for the designation of bosentan as an orphan-drug (application #00-1342). Please also refer to your submission dated August 30, 2000.

We have completed the review of this application and have determined that bosentan qualifies for orphan designation as treatment of pulmonary arterial hypertension.

Please be advised that if bosentan is approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA (21 U.S.C. 360cc). Therefore, prior to final marketing approval, sponsors of designated orphan drugs are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of bosentan as designated. Also an annual progress report must be submitted within 14 months after the designation date and annually thereafter until a marketing application is approved (21 CFR 316.30). If you need further assistance in the development of your product for marketing, please feel free to contact Tan T. Nguyen, M.D. at (301) 827-3666.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan-drug designation.

Sincerely yours,

/S/

Marlene E. Haffner, M.D., M.P.H.
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

TOTAL P.02

[redacted]

DEPARTMENT OF HEALTH & HUMAN SERVICES

McDonald

Food and Drug Administration
Rockville MD 20857

OCT 3 2000

NDA 21-290

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

Dear Dr. Hermann:

We have received your presubmission of chemistry and pharmacology information for the following:

Name of Drug Product: Bosentan (62.5 mg and 125 mg) Tablets

Date of Submission: September 25, 2000

Date of Receipt: September 25, 2000

Our Reference Number: NDA 21-290

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete. Please cite the NDA number assigned to this application at the top of the first page of every communication concerning this application.

Address all additional pre-submissions 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: Division Document Room
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: Division Document Room
1451 Rockville Pike
Rockville, Maryland 20852-1420

The submission that completes this application and is intended to start the review clock should be sent to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Ave.
Rockville, Maryland 20852-1833

If you have any questions, please call:

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

Sincerely,

/S/

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research