CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-290

Chemistry Review(s)

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls (CMC) section of an Application

NDA #: 21-290 **DATE OF REVIEW: 4-SEPTEMBER-2001**

REVIEW #: 2 **REVIEWER: Rajendra Uppoor, Ph.D., R.Ph.**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Presubmission	25-SEP-2000	25-SEP-2000	02-MAR-2001
Presubmission, NC	11-OCT-2000	16-OCT-2000	02-MAR-2001
~~Original~~	~~17-NOV-2000~~	~~17-NOV-2000~~	~~02-MAR-2001~~
Amendment, N-BC	05-MAR-2001	09-MAR-2001	12-MAR-2001
Amendment, N-BC	31-MAY-2001	05-JUN-2001	08-JUN-2001
Amendment, by e-mail	24-JUL-2001	[Print versions are requested	24-JUL-2001
Amendment, by e-mail	25-JUL-2001	as of August 20, 2001]	25-JUL-2001
Amendment, hand delivered	04-AUG-2001	20-AUG-2001	06-AUG-2001
Amendment, N-BC	16-AUG-2001	17-AUG-2001	21-AUG-2001
Amendment, by e-mail	17-AUG-2001	-	17-AUG-2001
Amendment, by fax	27-AUG-2001	-	27-AUG-2001
Amendment, e-mail, 11:42 am	29-AUG-2001	-	29-AUG-2001
Amendment, e-mail, 11:59 am	29-AUG-2001	-	29-AUG-2001
Amendment, e-mail, 4:15 pm	29-AUG-2001	**Note: Print versions of all e-mail**	29-AUG-2001
Amendment, e-mail, 10:38 pm	30-AUG-2001	**amendments have been requested**	30-AUG-2001
Amendment, e-mail, 9:27 am	31-AUG-2001	**from the applicant.**	31-AUG-2001

NAME & ADDRESS OF APPLICANT:

Actelion Limited
Gewerbestrasse 16, Allschwil
CH-4123, Switzerland.

Authorized US Agent:

Contact:

DRUG PRODUCT NAME

Proprietary: TRACLEER™
Established: Bosentan tablets
Code Name/#: Ro 47-0203/V18 for 62.5 mg Tablets
Ro 47-0203/V19 for 125 mg Tablets

Chem. Type/Ther. Class: 1 S

Designated as an **Orphan Drug?**	**Yes.**
PHARMACOL. CATEGORY/INDICATION:	Used in the treatment of Primary Pulmonary Hypertension.
DOSAGE FORM:	Film coated tablets.
STRENGTHS:	62.5 mg Bosentan/Tablet and 125 mg Bosentan/Tablet.
ROUTE OF ADMINISTRATION:	Oral.
Rx/OTC:	X Rx ___ OTC
SPECIAL PRODUCTS:	___ Yes X No

(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

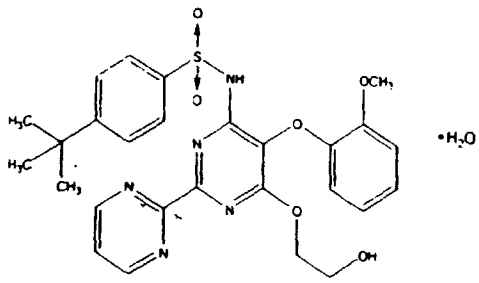
Chemical Abstracts Index Name:
Benzenesulfonamide, 4-(1,1-dimethylethyl)-N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)[2,2'-bipyrimidin]-4-yl]-, monohydrate. **CAS registry #:** 157212-55-0.

Other Names:
4-*tert*-Butyl-*N*-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-[2,2']-bipyrimidinyl-4-yl]-benzenesulfonamide, monohydrate.

p-*tert*-Butyl-*N*-[6-(2-hydroxy-ethoxy)-5-(*o*-methoxy-phenoxy)-2-(2-pyrimidinyl)-4-pyrimidinyl]-benzenesulfonamide, monohydrate.

Generic (INN) Name: Bosentan [USAN has adopted this name for the monohydrate form].

Structural Formula:



Molecular Formula: $C_{27}H_{29}N_5O_6S \bullet H_2O$. **Relative Molecular Mass: 569.64.**

SUPPORTING DOCUMENTS:

DMF # and Type	Subject	Holder	Status	Review Date	Letter Date
			Adequate.	4/30/01	-
			Adequate.	8/17/01	-
			Adequate.	8/13/01	-
			Adequate.	8/15/01	-
			Adequate.	8/17/01	-
			Adequate.	3/4/99	-

RELATED DOCUMENTS (if applicable):

IND
IND

CONSULTS:

Office of Clinical Pharmacology and Biopharmaceutics (OCPB):

The CDER/OCPB review team was consulted for reviewing the dissolution medium, dissolution method and dissolution specification (acceptance criteria) proposed in applicant's amendment dated August 16, 2001. The OCPB review team has recommended a change in the dissolution medium that should be used for the dissolution testing of drug products.

Comments by chemistry reviewer:

The OCPB's review team's recommendation should be communicated to the applicant.

REVIEW SUMMARY

At the completion of this CMC Review # 2, deficiencies that were identified in CMC Review # 1 [completed on 8/22/2001] with respect to drug substance and drug product sections of this application and its amendments have been resolved satisfactorily. The applicant has submitted data to demonstrate that the drug products proposed for marketing in this application are satisfactory with respect to their identity, strength, quality and purity. Drug product labels and labeling information related to drug products' DESCRIPTION, HOW SUPPLIED, and STORAGE sections are adequate. An expiration

dating period of **months** can be recommended for both 62.5 mg and 125 mg strengths of TRACLEER® (bosentan) tablets at this time.

An acceptable overall recommendation has been received from the CDER Office of Compliance for pre-approval inspections of all manufacturing and testing facilities involved the manufacturing of drug substance intermediates, drug substance, and drug products submitted in this application. Validation of analytical procedures described in the application for testing drug substance and drug products at FDA laboratories is **pending** at this time.

CONCLUSION & RECOMMENDATIONS:

Based on data submitted to demonstrate the identity, strength, quality and purity of the drug substance and the drug products proposed for marketing in this application and its amendments, this application is recommended for an **APPROVAL** action from the CMC review point of view. The OCPB review team's outstanding recommendations should be communicated to the applicant. Validation of analytical methods at FDA laboratories is pending at this time, and applicant's continued cooperation to satisfactorily complete this method validation should be requested.

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Rajendra Uppoor, Ph.D., R.Ph.
Review Chemist

S

Kasturi Srinivasachar, Ph.D.
Chemistry Team Leader

cc:

Original NDA 21-290
HFD-110/Division File
HFD-150/Rev.Chemist/R. Uppoor
HFD-#110/Chem.Team Leader/K. Srinivasachar
HFD-810/Dep.Division Director/H.B. Patel
HFD-810/Chemistry Division Director/J. Simmons (NMEs only)
HFD-110/Proj.Manager/Z. McDonald

R/D Init. by: TEAMLEADER

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DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls (CMC) section of an Application

NDA #: 21-290 **DATE OF REVIEW:** 20-AUG-2001

REVIEW #: 1 **REVIEWER:** Rajendra Uppoor, Ph.D., R.Ph.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Presubmission	25-SEP-2000	25-SEP-2000	02-MAR-2001
Presubmission, NC	11-OCT-2000	16-OCT-2000	02-MAR-2001
Original	17-NOV-2000	17-NOV-2000	02-MAR-2001
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Amendment, hand delivered	04-AUG-2001	20-AUG-2001	06-AUG-2001

NAME & ADDRESS OF APPLICANT: Actelion Limited
Gewerbestrasse 16, Allschwill
CH-4123, Switzerland.

Authorized US Agent:

Contact:

DRUG PRODUCT NAME

Proprietary:	TRACLEER™
Established:	Bosentan tablets
Code Name/#:	Ro 47-0203/V18 for 62.5 mg Tablets Ro 47-0203/V19 for 125 mg Tablets
Chem. Type/Ther. Class:	**1 S**
Designated as an **Orphan Drug**?	**Yes.**

PHARMACOL. CATEGORY/INDICATION: Used in the treatment of Primary Pulmonary Hypertension.

DOSAGE FORM: Film coated tablets.

STRENGTHS: 62.5 mg Bosentan/Tablet and
125 mg Bosentan/Tablet.

ROUTE OF ADMINISTRATION: Oral.

Rx/OTC: X Rx ___ OTC

SPECIAL PRODUCTS: ___ Yes _X_ No
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

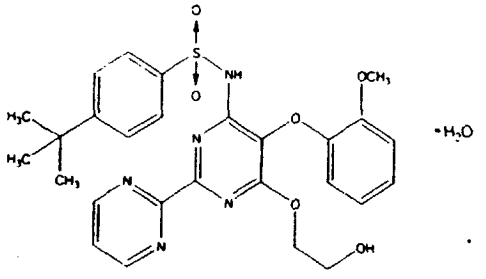
Chemical Abstracts Index Name:
Benzenesulfonamide, 4-(1,1-dimethylethyl)-N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)[2,2'-bipyrimidin]-4-yl]-, monohydrate. **CAS registry #:** 157212-55-0.

Other Names:
4-*tert*-Butyl-*N*-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-[2,2']-bipyrimidinyl-4-yl]-benzenesulfonamide, monohydrate.

p-*tert*-Butyl-*N*-[6-(2-hydroxy-ethoxy)-5-(*o*-methoxy-phenoxy)-2-(2-pyrimidinyl)-4-pyrimidinyl]-benzenesulfonamide, monohydrate.

Generic (INN) Name: Bosentan [USAN has adopted this name for the monohydrate form].

Structural Formula:



Molecular Formula: $C_{27}H_{29}N_5O_6S \bullet H_2O$. Relative Molecular Mass: 569.64.

SUPPORTING DOCUMENTS:

DMF # and Type	Subject	Holder	Status	Review Date	Letter Date
[redacted]			Adequate.	4/30/01	-
			Adequate.	8/17/01	-
			Adequate.	8/13/01	-
			Adequate.	8/15/01	-

DMF # and Type	Subject	Holder	Status	Review Date	Letter Date
			Adequate.	8/17/01	-

RELATED DOCUMENTS (if applicable):

IND[ ]
IND[ ]

CONSULTS:

Office of Clinical Pharmacology and Biopharmaceutics (OCPB):

The OCPB was consulted for reviewing the dissolution method and dissolution specification proposed in the application. The OCPB finds the sponsor proposed dissolution medium and specifications **not acceptable,** and has recommended revisions. The OCPB review recommendations are listed in the Drug Product "Regulatory Specifications and Methods" section (see page 58) of this review.

Comments by chemistry reviewer:

This chemistry reviewer concurs with the recommendations made by the biopharmaceutics reviewer. The OCPB recommended revisions were communicated to the applicant on 8/9/2001.

Office of Post-Marketing and Drug Review & Analysis (OPDRA):

OPDRA has no objections to the use of the proprietary name, "Tracleer".

In OPDRA's review dated February 8, 2001 has recommended six revisions in the container label for implementation to minimize potential errors with the use of the proposed drug product. They are stated below:

1. OPDRA recommends that the established name be printed in letters that are at least half as large as the letters comprising the proprietary name to be in accordance with 21 CFR 201.10(g)(2).
2. In order to prevent medication errors due to the similarity in labeling among the two strengths, OPDRA recommends differentiating the labels for the different strengths (e.g. different colors and/or boxing).
3. The established name should be revised to read: Bosentan Tablets.
4. On the draft container, OPDRA recommends adding the net quantity, 60 tablets.
5. Revise the following: Each tablet contains XX mg of bosentan monohydrate.
6. Revise the usual dosage statement to read: "Usual Dosage: One tablet twice daily. See package Insert".

Comments by chemistry reviewer:

From the chemistry review point of view, this chemistry reviewer concurs with OPDRA reviewer's recommendations 1, 2, 3 and 4 above. With respect to item 5, this reviewer is of the opinion that an asterisk (*) should be placed after 62.5 and 125 on the drug product labels. On the side panel of the TRACLEER™ 62.5 mg bottle label, it should be stated that "* Each tablet contains 64.541 mg of bosentan, equivalent to 62.5 mg of anhydrous bosentan". On the side panel of the TRACLEER™ 125 mg bottle label, it should be stated that "* Each tablet contains 129.082 mg of bosentan, equivalent to 125 mg of anhydrous bosentan". This is in view of USAN nomenclature for bosentan, which includes one molecule of water of hydration in the structure of bosentan [see USP Dictionary of USAN and International Drug Names, 1996 and beyond]. Item 6 of OPDRA reviewer's recommendation is outside the scope of this chemistry reviewer's comment.

OPDRA's recommendations have been communicated to the applicant on 8/9/2001.

REVIEW SUMMARY:

At the completion of this CMC Review # 1, deficiencies have been identified in both drug substance and drug product sections of this application. The deficiencies relate to incomplete information on the [s methods, incomplete information on drug substance. Deficiencies also include incomplete ; used in the analysis of] .

Deficiencies identified in the drug product section include incorrect and incomplete information provided in the [ ] records. Additional information on in-process testing of granules, reporting of stability results, and design of stability studies for post-approval batches will be required. Some changes will be required in the proposed regulatory test procedures and acceptance criteria for individual and total unspecified, unidentified degradation products. Changes in test methods and acceptance criteria for dissolution testing of tablets will be required. Additional information is needed on some of the components used in the packaging of drug products.

Changes will be needed in the proposed labels of drug products and labeling information submitted in the proposed packaging insert. Based on only (\months stability data and no statistical analyses submitted in the application, an **expiration dating period of** (**months** can be recommended for the drug products at this time.

CMC deficiencies observed in the application were communicated to the applicant in a meeting held on August 9, 2001 as comments and request for additional information during this on-going review period. Applicant's responses to deficiencies communicated to them will be reviewed expeditiously in subsequent CMC review(s).

Requests for validation of analytical procedures used in testing of drug substance and drug products will be sent to FDA laboratories after resolving the deficiencies that have been identified. An **acceptable**

overall recommendation has been received from the CDER Office of Compliance for pre-approval inspections of all manufacturing and testing facilities involved in the manufacturing of drug substance intermediates, drug substance, and drug products submitted in the application.

CONCLUSION & RECOMMENDATIONS:

Deficiencies have been identified in the CMC sections of drug substance and drug product portions of this application. They have been communicated to the applicant as of August 9, 2001. The applicant has agreed to submit additional information to the application to resolve the deficiencies in an expeditious manner. Therefore, from the CMC review perspective, this application is recommended for a **NOT APPROVABLE** action until satisfactory responses to all deficiencies will be received from the applicant.

/S/

Rajendra Uppoor, Ph.D., R.Ph.
Review Chemist

/S/

Kasturi Srinivasachar, Ph.D.
Chemistry Team Leader

cc:

Original NDA 21-290
HFD-110/Division File
HFD-150/Rev.Chemist/R.Uppoor
HFD-110/Proj.Manager/Z.McDonald
HFD-#110/Chem.Team Leader/K. Srinivasachar
HFD-810/Chemistry Division Director/J. Simmons (NMEs only)

R/D Init. by: TEAMLEADER

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ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21290/000
Stamp: 17-NOV-2000
Regulatory Due: 17-SEP-2001
Applicant: ACTELION
4123 ALLSCHWIL
, , SZ
Priority: 1S
Org Code: 110

Action Goal:
District Goal: 19-JUL-2001
Brand Name: BOSENTAN 62.5MG/125MG TABLETS
Estab. Name:
Generic Name: BOSENTAN 62.5MG/125MG TABLETS

Dosage Form: (TABLET)
Strength: 62.5 AND 125 MG

Application Comment:
FDA Contacts: Z. MCDONALD (HFD-110) 301-594-5300 , Project Manager
J. ADVANI (HFD-110) 301-594-5300 , Review Chemist
K. SRINIVASACHAR (HFD-110) 301-594-5376 , Team Leader

Overall Recommendation: ACCEPTABLE on 19-JUL-2001 by S. ADAMS (HFD-324) 301-594-0095

Establishment:

DMF No:
Responsibilities:
Profile: CRU
Estab. Comment:

AADA:
OAI Status: NONE

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	03-OCT-2000				ADVANIJ
OC RECOMMENDATION	04-OCT-2000			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment:

DMF No:
Responsibilities:
Profile: CRU
Estab. Comment:

AADA:
OAI Status: NONE

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	03-OCT-2000				ADVANIJ
OC RECOMMENDATION	04-OCT-2000			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment:

DMF No:
Responsibilities:
Profile: CTL
Estab. Comment:

AADA:
OAI Status: NONE

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	03-OCT-2000				ADVANIJ
SUBMITTED TO DO	04-OCT-2000	GMP			FERGUSONS
ASSIGNED INSPECTION	12-OCT-2000	GMP			EGASM
INSPECTION SCHEDULED	07-NOV-2000		10-NOV-2000		IRIVERA

INSPECTION PERFORMED	06-APR-2001	10-NOV-2000		EGASM
DO RECOMMENDATION	06-APR-2001		ACCEPTABLE	EGASM
OC RECOMMENDATION	06-APR-2001		INSPECTION ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

Establishment: 9690045
PATHEON INC
MISSISSAUGA, ONTARIO, CA L5N 7K9
DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER
Profile: TCM OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	03-OCT-2000				ADVANIJ
SUBMITTED TO DO	04-OCT-2000	PS			FERGUSONS
ASSIGNED INSPECTION	17-OCT-2000	PS			EGASM
INSPECTION SCHEDULED	22-FEB-2001		23-MAR-2001		IRIVERA
INSPECTION PERFORMED	23-MAR-2001		22-MAR-2001		EGASM
DO RECOMMENDATION	14-JUN-2001			ACCEPTABLE	DAMBROGIOJ
OC RECOMMENDATION	14-JUN-2001			INSPECTION ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment:

DMF No: AADA:
Responsibilities:
Profile: CRU OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	03-OCT-2000				ADVANIJ
SUBMITTED TO DO	04-OCT-2000	GMP			FERGUSONS
DO RECOMMENDATION	26-JAN-2001			ACCEPTABLE BASED ON FILE REVIEW	EGASM
OC RECOMMENDATION	26-JAN-2001			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

Establishment:

DMF No: AADA:
Responsibilities:
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	03-OCT-2000				ADVANIJ
SUBMITTED TO DO	04-OCT-2000	GMP			FERGUSONS

ASSIGNED INSPECTION	12-OCT-2000 GMP			EGASM
INSPECTION SCHEDULED	25-APR-2001	30-MAY-2001		IRIVERA
INSPECTION PERFORMED	01-JUN-2001	30-MAY-2001		EGASM
DO RECOMMENDATION	19-JUL-2001		ACCEPTABLE	ADAMSS
			INSPECTION	
OC RECOMMENDATION	19-JUL-2001		ACCEPTABLE	ADAMSS
			DISTRICT RECOMMENDATION	

APPEARS THIS WAY
ON ORIGINAL

CLAIM OF CATEGORICAL EXCLUSION

In accordance with 21 CFR 25.31(b), this claim of categorical exclusion is based on the calculation which shows that the estimated concentration of the active moiety, bosentan, at the point of entry into the aquatic environment due to use at the fifth-year of marketing will be below 1 part per billion (ppb).

The calculation was based on the following assumptions and equation as stated in the FDA Guidance for Industry, *Environmental Assessment of Human Drug and Biologics Applications* (July 1998).

The expected introduction concentration (EIC) of an active moiety into the aquatic environment was calculated as follows:

EIC-Aquatic (ppb) = A x B x C x D where

A = kg/year produced for direct use (as active moiety). Current marketing projections anticipate 819.2 kg of bosentan active moiety to be produced in the fifth-year of marketing

B = l/liters per day entering publicly owned treatment works. Which according to 1996 Needs Survey, Report to Congress, is 1.214×10^{11} liters per day

C = year/365 days

D = 10^9 µg/kg (conversion factor)

$$\text{EIC-Aquatic} = \frac{8.192 \times 10^2 \text{ kg} \times 10^9 \text{ µg/kg}}{1.214 \times 10^{11} \text{ l/d} \times 365} = 0.0185 \text{ ppb}$$

Therefore, with respect to compliance with the categorical exclusion criteria to the best of my knowledge, no extraordinary circumstances exist.