

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209279Orig1s000

OTHER REVIEW(S)



DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Overview

I. GENERAL INFORMATION

NDA: 209279

Drug: Tracleer® (bosentan) 32 mg

Dosage Form: Dipersible Tablets

Class: endothelin receptor antagonist

Applicant: Actelion Pharmaceuticals, Ltd.

Proposed Indications: Pulmonary Arterial Hypertension (WHO Group 1)

Date of submission: August 5, 2016

Review extension letter: May 23, 2017

PDUFA date: September 5, 2017

Target Action date: September 5, 2017

II. REVIEW TEAM

Office of New Drugs, Office of Drug Evaluation I:

Division of Cardiovascular & Renal Product

Division Director: Norman Stockbridge, MD, PhD

CDTL and Clinical Team Leader: Aliza Thompson, MD, MS

Clinical reviewer: Maryann Gordon, MD

Pharmacology/Toxicology Team Lead: Albert Defelice, PhD

Pharmacology/Toxicology: John Koerner, PhD

Clinical Analyst: Christine Garnett, PharmD

Regulatory Project Manager: Maryam Kord Bacheh Changi, PharmD

Office of Pharmaceutical Quality:

Product Quality ATL: Mohan Sapru, PhD

Branch Chief: Wendy Wilson, PhD

Drug substance: N/A

Drug Product: Stephanie Emory, PhD

Biopharmaceutics: Joan Zhao, PhD

Facility: Zhong Li, PhD

Process: Peter Guerreier, PhD

Office of Biostatistics, Division of Biometrics I:

Jialu Zhang, PhD

Office of Clinical Pharmacology:

Sudharshan Hariharan, PhD

Venkateswaran Chithambaram Pillai, PhD

Jeffrey Florian, PhD

Office of Surveillance and Epidemiology:

DPV: N/A

DMEPA: Sarah Thomas

DRISK: Jacqueline Sheppard, PharmD; Theresa Ng, PharmD

Office of Prescription Drug Promotion:

Puja Shah, PharmD

Division of Pediatric and Maternal Health:

Jane Liedtka, MD

III. BACKGROUND

This NDA references IND 058317 and NDA 021290, for the use of bosentan in patients with pulmonary arterial hypertension (PAH). The IND was submitted by Actelion on 08 May 1999. The NDA was submitted by Actelion on 17 November 2000 and approved by the Agency on 20 November 2001. The proposed labeling for the subject application is based on the current and approved labeling for NDA 021290 for TRACLEER (bosentan) film-coated tablets.

Actelion submitted two patent claims, Patent claims drug product which expires May 12, 2026 and December 28, 2027.

Actelion also submitted claims exclusivity under 21 CFR 314.108 and 21 CFR 316.31:

- Consistent with 21 CFR 314.108(b)(4), the sponsor is of the opinion that this application (NDA 209279) is eligible for 3 years of market exclusivity.
- Consistent with 21 CFR 316.31, the sponsor is of the opinion that this application (NDA 209279) is eligible for 7 years of orphan drug exclusivity. The sponsor referenced Reference the orphan designation granted for bosentan (October 6, 2000) for the treatment of pulmonary arterial hypertension (designation number 00-1342).

On April 4, 2017 the sponsor submitted CMC major amendment which led to extending clock for 3 months.

IV. APPLICATION REVIEW**1. User Fee**

The User fee for this application was paid in full on July 7, 2016. User Fee I.D. Number for this application is PD3016119.

2. Pediatric Review Committee (PeRC):

This NDA does not trigger PREA, this product has Orphan Designation. The PeRC meeting was not needed.

3. Review Status:

NDA 209279 was considered a Standard Review (10-month clock). On May 23, 2017, the Division issued the clock extension letter based on the Major CMC amendment (received April 2017).

4. Advisory Committee:

There was no Advisory Committee meeting for this NDA because it did not raise any significant safety or efficacy issues.

5. Trade name

Per the July 14, 2017 proprietary name submission, Actelion has obtained the trademark Tracleer. The proposed proprietary name is acceptable.

6. Facilities Inspections:

- The Office of Process and Facilities has recommended overall approval for the Manufacturing facilities (refer to OPQ review dated August 8, 2017).
- One domestic site clinical investigator (Dunbar Ivy, Colorado) was inspected in support of NDA 209279. Although regulatory violations were found during the inspection, they were unlikely to impact the outcome of the study or the reliability of the data submitted to support approval for the indication. Based on the results of this inspection, OSI recommended that the data submitted by the sponsor in support of the pending application from this site are acceptable and the study was conducted adequately to support approval. (Please refer to OSI review dated May 11, 2017).

7. Regulatory Timeline:

Pre sNDA Meeting: July 22, 2015
NDA Receipt date: August 5, 2016
Filing date: October 4, 2016
74- Day letter: October 18, 2016
Mid-Cycle meeting: January 12, 2017
Proprietary name accepted: N/A
Advisory committee: N/A
Major Amendment received: April 4, 2017
Clock extension letter: May 23, 2017
PDUFA Date: September 5, 2017 (after 3 months extension)
Approval letter: September 5, 2017

Reviews

a) Divisional Memorandum – September 4, 2017

Dr. Stockbridge indicated his concurrence on Dr. Thompson's CDTL memo.

b) Cross-Discipline Team Leader Review- September 4, 2017

Dr. Thompson recommends approval. Her review summarizes each disciplines findings including consults. She also provided a detailed regulatory history.

c) Clinical Pharmacology Review- April 11, 2017

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the pharmacokinetic information submitted in this NDA. The review team proposes dosing table based on body weight bands that allow only bisection of the scored dispersible tablet to overcome any potential product issues that might arise with quadrisecting the tablet.

For an evaluation of efficacy supporting this application, please refer to review by Drs. Garnet and Florian (NDA 209279, DARRTS date: 03/31/2017).

d) Pharmacology & Toxicology Review- March 20, 2017

Bosentan was evaluated in a juvenile toxicity study in rats, with oral dosing by gavage started on postpartum day 4, and continued thru postpartum day 69, or thru mating on postpartum day 84. Dosages evaluated in this study were 0, 15, 45, 135 mg/kg/day, with dosages based on a dose- range finding study in rats. General toxicology was evaluated – mortality, body weight, organ weights and histopathology - along with behavior and learning, and reproduction (fertility, resorptions, corpora lutea, live and dead embryos).

e) Office of Pharmaceutical Quality Review- August 7, 2017

An integrated summary was written by Dr. Sapru for product quality. Approval is recommended from the quality perspective.

8. Consults

Please see the following reviews and their corresponding dates:

- OSE/DMEPA: March 08, 2017; August 16, 2017; August 31, 2017
- OPDP: March 20, 2017
- Patient Labeling (Instructions for Use): April 27, 2017
- DPMH: March 30, 2017
- OSI: May 11, 2017
- OSIS: November 23, 2016
- DRISK: June 2, 2017; September 1, 2017
- Ethics: January 12, 2017

9. Labeling

Labeling discussions occurred with the applicant. The final agreed-upon labeling will be attached to the approval letter.

DRISK review dated June 2, 2017 for Evaluation of proposed REMS modification to Tracleer for the proposed indication of pulmonary arterial hypertension in pediatric patients and a new dispersible tablet formulation. DRISK did not agree with all of the Actelion's proposals for the REMS submitted under NDA 209279. Comments were sent to the sponsor. Actelion amended the REMS on August 8 and 25, 2017.

On September 1, 2017, DRISK finds the proposed REMS and REMS materials for Tracleer (bosentan) NDA 209279 as submitted on August 25, 2017 to be acceptable.

On August 29, 2017 the Division requests a t-con with Actelion to discuss the labeling of the Tracleer (bosentan) 32 mg tablets for oral suspension, Actelion agreed to use the version of the blister strip label that was sent in advance of the meeting with version number 1372 (attached to the approval letter).

Actelion suggested, via email communication, which if other manufacturers are able to produce readable barcodes of the suggested size, as has been the Agency's experience as communicated during the t-con, they will be able to do the same. Actelion also ensured the Agency that if they receive customer complaints about the ability to scan these codes post marketing, they will undertake an immediate effort to develop packaging that is larger and can accommodate larger barcodes. The Agency found the approach reasonable and agreed that Actelion should let the Agency know the results of their readability testing.

V. CONCLUSION:

The review team recommended approval.

The Approval Letter was signed by Dr. Norman Stockbridge, Director, Division of Cardiovascular and Renal Products on September 5, 2017.

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/s/

MARYAM K CHANGI
09/05/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 31, 2017
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 209279
Product Name and Strength:	Tracleer (bosentan) Tablet for Oral Suspension, 32 mg
Applicant/Sponsor Name:	Actelion Pharmaceuticals LTD
Submission Date:	August 22, 2017 and August 30, 2017 ¹
OSE RCM #:	2016-1918-2
DMEPA Primary Reviewer:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS
DMEPA Associate Director (Acting):	Danielle Harris, PharmD, BCPS

¹ The revised, proposed container labels were submitted from Actelion by email and not via eCTD submission to DARRTS at the time of this memo.

1 PURPOSE OF MEMO

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container labels submitted on August 30, 2017 and the revised carton labeling submitted on August 22, 2017 for Tracleer (bosentan) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a prior label and labeling review.²

2 CONCLUSION

Our review of the proposed container labels and carton labeling found Actelion addressed most of our recommendations from our previous review. We note that Actelion was able to include the bar code and other important information (e.g., proprietary and established names, strength, lot number and expiration date) on each blister cell label by decreasing the size of the bar code and relocating the phenylketonurics statement and manufacturer name to the middle blister cell. We find these revisions acceptable, especially since the middle blister cell does not contain a tablet. Actelion reported in their August 30, 2017 email communication that the smaller bar code still requires readability testing, and they will inform FDA of the results once available. Actelion stated if they receive customer post-market complaints about the ability to scan the blister label bar codes, then they will undertake immediate effort to develop larger blister packaging that can accommodate larger, readable bar codes. We find the proposed Tracleer container labels, proposed carton labeling, and Actelion's proposed plan acceptable, and we have no further recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

² Thomas, S. Label and Labeling Review Memo for Tracleer (bosentan) Tablet for Oral Suspension (NDA 209279). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 AUG 16. RCM No.: 2016-1918-1.

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/s/

SARAH E THOMAS
08/31/2017

CHI-MING TU
08/31/2017

DANIELLE M HARRIS
08/31/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 16, 2017
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 209279
Product Name and Strength:	Tracleer (bosentan) Tablet for Oral Suspension, 32 mg
Applicant/Sponsor Name:	Actelion Pharmaceuticals LTD
Submission Date:	April 14, 2017 and June 6, 2017
OSE RCM #:	2016-1918-1
DMEPA Primary Reviewer:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS
DMEPA Associate Director (Acting):	Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container label, carton labeling, prescribing information, and medication guide for Tracleer (bosentan) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION

After reviewing the revised container label, carton labeling, prescribing information (PI), and medication guide for Tracleer, we note Actelion addressed most of our recommendations from our previous review. However, some outstanding issues remained, thus we discuss them below:

¹Thomas, S. Label and Labeling Review for Tracleer (bosentan) Tablet for Oral Suspension (NDA 209279). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 March 8. RCM No.: 2016-1918.

A. Container Label and Carton Labeling

We note that Actelion did not incorporate our recommendation to revise the strength presentation on the blister cell labels and carton labeling to describe the milligram amount of drug per single blister unit (32 mg per tablet for oral suspension). Actelion points to the statement “Each tablet contains 32 mg of anhydrous bosentan” on the side panel of the carton labeling, and the space constraints on the blister container labels. We find Actelion’s rationale acceptable.

We also note that LOT and EXP designations are being removed from the end panel in (b) (4) and that the storage and preparation information need updating to align with the storage and preparation information provided in the prescribing information. Also, we note the revised blister container label submitted June 6, 2017 does not contain a barcode and other important information (e.g., proprietary and established names, strength, lot number and expiration date) on each blister cell label. We provide recommendations related to these points in Section 3 below.

B. Prescribing Information and Medication Guide

(b) (4) tablet scores

(b) (4)

suspension will again only require splitting the 32 mg tablet in half for oral suspension. We note that the (b) (4) does not align with the Clinical Pharmacology recommended dosing of 16 mg, 32 mg, 48 mg, and 64 mg (e.g., ½ tablet, 1 tablet, 1.5 tablets, and 2 tablets, respectively). Specifically, end users would only need to split the tablet in half (b) (4) to achieve the aforementioned doses. Per CMC’s review of the scoring data submitted to FDA, the tablet is able to be functionally split in halves (b) (4). We acknowledge that the (b) (4) may be error-prone now that dosing has been revised. However, given the proposed dosing doesn’t instruct splitting the tablet into (b) (4) and the public health need of this proposed dosage form to accommodate pediatric dosing, we do not object to the (b) (4) on the proposed

tablet for oral suspension. In addition, DCRP has added warnings in the PI and Medication Guide to not split the tablets into quarters.

Storage for leftover tablet pieces

We note in response to our concern regarding blister packaging not allowing for storage of leftover tablet pieces, Actelion added a statement to sections 2.3 and 16 and the Medication Guide that “tablet pieces may be returned to the opened blister and stored there for up to 7 days.” This language of storing the broken tablet pieces in the opened blister may promote a storage practice that increases the likelihood of a child inadvertently ingesting the broken pieces and experiencing an accidental overdose. DMEPA suggested a revision in language to the following: “Tablet pieces may be returned to the open blister and stored there out of reach of children for up to 7 days.” We note that Actelion accepted our proposal.

Volume to dissolve the tablet for oral suspension

In response to our concern regarding lack of administration instructions for the tablet for oral suspension (e.g., how much water to dissolve the tablet for oral suspension or tablet pieces prior to administration), Actelion added instructions to Section 2.3 to (b) (4). “According to Actelion, this is based on a study of (b) (4). Because a measurement device for this (b) (4) volume may not be readily available to end users of the proposed product, DMEPA brought this to the review team’s attention. After discussion, the review team decided to change the “(b) (4)” to “a minimal amount.”

3 RECOMMENDATIONS FOR ACTELION PHARMACEUTICALS LTD

We recommend the following be considered and/or implemented prior to approval of this NDA:

A. Container Label and Carton Labeling

1. Your June 6, 2017 submission stated the preprinted words LOT and EXP are being removed from the end panel in preparation for serialization of this product per FDA regulation. We understand you intend to print the lot and expiration date inline at the time of packaging. Ensure that the LOT and EXP are clearly differentiated from one another and from other numbers that can be for the lot and expiration date, such as by clearly labeling the lot number as “LOT” and expiration date as “EXP”.²

B. Container Labels

1. Your revised blister container label submitted June 6, 2017 does not contain a barcode on each blister cell. As proposed, we are concerned that the barcode and other important information, like the proprietary and established names, strength, lot number and expiration date, will not remain available to the end user up to the point at which the last dose is removed because the blister cells

² Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert A cute Care. 2014;19(23):1-4.

are divided by perforations that enable the cells to be separated.³ A barcode should be placed on the immediate container label per 21 CFR 201.25. Revise the blister container label to include a barcode, proprietary and established names, strength, lot number and expiration date on each blister cell. We acknowledge the space constraint. Thus we advise you to explore a design that allows for a barcode of an adequate size that fits on each blister cell along with other important information like the proprietary and established names, the strength, manufacturer name, lot number and expiration date. For example, consider abbreviating the Phenylketonuric statement to read “Phenylketonurics: Contains Phenylalanine.” In addition, because there are 14 tablets per blister strip and 15 blister labels, we recommend reformatting the label of the empty blister cell to communicate to the end user that there is no tablet for oral suspension in that particular blister.

C. Carton Labeling

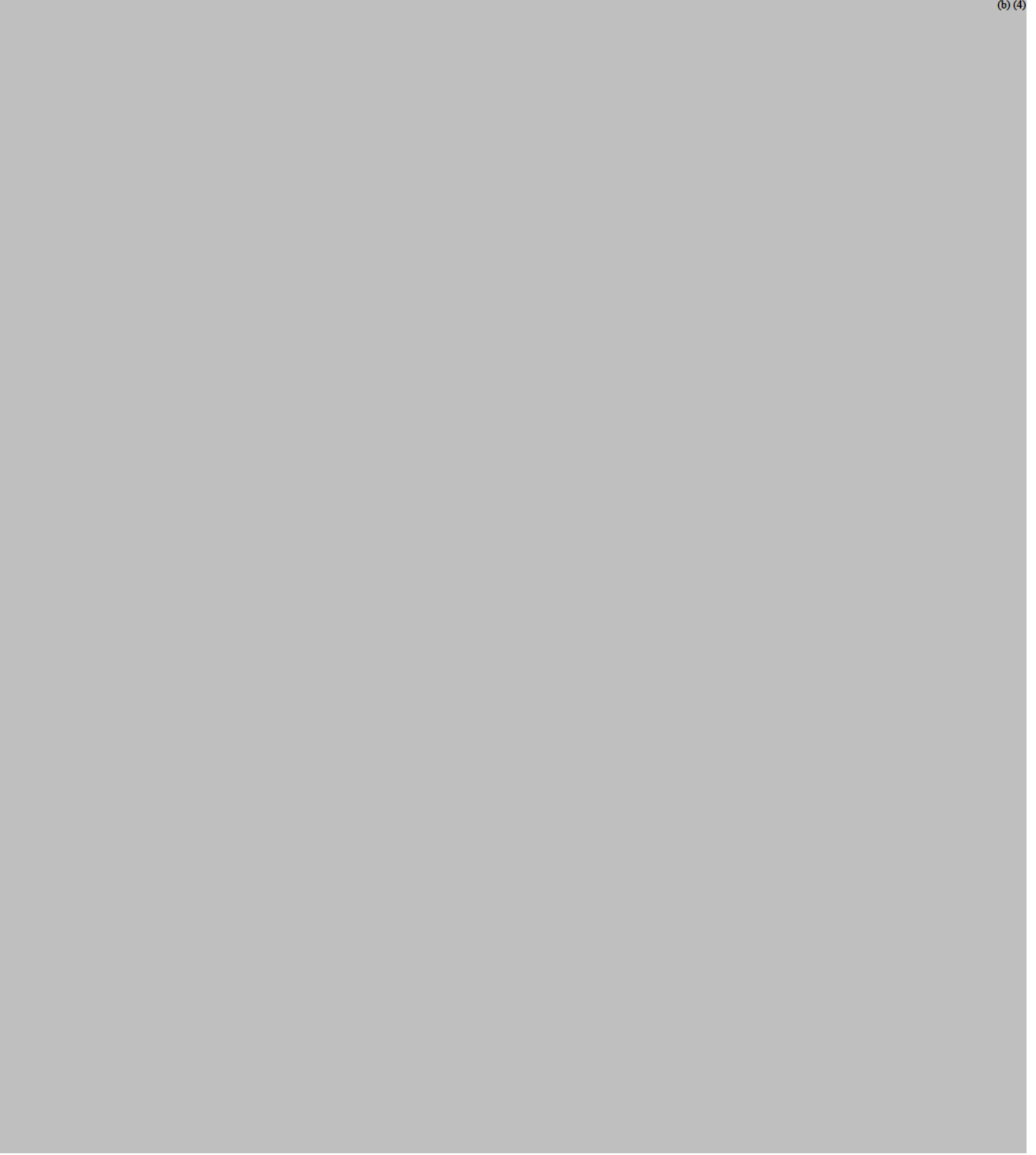
1. We recommend that Actelion revise the additional storage information for the leftover pieces of tablets for oral suspension to align with that provided in the PI, as follows:
“Divided tablets for oral suspension should be stored at 20°C – 25°C (68°F – 77°F) and used within 7 days. Tablet pieces may be returned to the opened blister and stored there out of reach of children for up to 7 days.”
2. We recommend that Actelion revise the added Usual Dosage instructions to align with that provided in the PI, as follows:
“Disperse tablets for oral suspension, or dispersible tablet half, in a minimal amount of water immediately before administration.”

³ See *Guidance for Industry: Bar Code Label Requirements Questions and Answers*. Available at: <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM267392.pdf>

APPENDIX A. LABEL AND LABELING SUBMITTED ON APRIL 14, 2017 AND JUNE 6, 2017

Container Label

(b) (4)



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/s/

SARAH E THOMAS
08/16/2017

CHI-MING TU
08/16/2017

DANIELLE M HARRIS
08/16/2017

Clinical Inspection Summary

Date	05/11/2017
From	Sharon Gershon, Pharm.D, Susan Thompson, M.D., Team Leader, Kassa Ayalew, M.D., M.P.H., Branch Chief, DCCE/GCPAB/OSI
To	Maryann Gordon, M.D, DCRP Clinical Reviewer Aliza Thompson, M.D, DCRP Team Leader Norman Stockbridge, M.D, DCRP Division Director Maryam Kord Bacheh Changi, DCRP Regulatory Health Project Manager Division of Cardiovascular and Renal Products (DCRP)
NDA #	NDA 209279
Applicant	Actelion Clinical Research, Inc.
Drug	TRACLEER® (bosentan) dispersible tablets
NME	No
Therapeutic Classification	Priority
Proposed Indication	Pediatric patients with pulmonary arterial hypertension
Consultation Request Date	October 26, 2016
Summary Goal Date	April 1, 2017, extended to May 10, 2017
Action Goal Date	June 4, 2017
PDUFA Date	June 5, 2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATION

One domestic site clinical investigator (Dunbar Ivy, Colorado) was inspected in support of NDA 209279. Dr. Dunbar Ivy's site enrolled ten subjects, and the results from this site drove the efficacy results, including findings for pulmonary vascular resistance (PVR). Study AC-052-356 (BREATHE-3), was a pharmacokinetic study conducted and submitted to FDA to support the PVR pharmacologic effect for approval of bosentan dispersible tablets. The proposed indication was for the treatment of pediatric patients < 12 years of age with pulmonary arterial hypertension (PAH), and the study provided for a new 32 mg dispersible tablet form of TRACLEER™. The rationale for site selection was high treatment responders and significant primary efficacy results pertinent to decision-making.

Although regulatory violations were found during the inspection, they are unlikely to impact the outcome of the study or the reliability of the data submitted to support approval for the indication. Based on the results of this inspection, OSI recommends that the data submitted by the sponsor in support of the pending application from this site are acceptable and the study was conducted adequately to support approval.

II. BACKGROUND

Actelion Pharmaceuticals Ltd submits this NDA for TRACLEER™ (bosentan) dispersible tablets. The purpose of the NDA submission is to provide for the use of TRACLEER™ (bosentan) in the treatment of pediatric patients < 12 years of age with pulmonary arterial hypertension (PAH), and to provide for a new 32 mg dispersible tablet form of TRACLEER™. The study was conducted between May 11, 2001 and February 13, 2002.

The efficacy evaluation in this NDA is based on ‘bridging’ of data between the adult and pediatric studies primarily utilizing the pivotal, Phase 3 trial AC-052-356 (BREATHE-3) in which pediatric patients (age 2-17 years) with PAH were dosed with 31.25 mg, 62.5 mg, and 125 mg bosentan film-coated tablets.

This was an open-label, non-controlled, parallel-group, three-arm study designed to assess the pharmacokinetics, tolerability, and safety of single and multiple oral doses of bosentan with stratification by subject weight and epoprostenol use. Secondary objectives were to obtain preliminary data on changes in hemodynamics, exercise capacity, Borg dyspnea index, and WHO functional class after three months in pediatric patients with PAH.

Previous results from clinical trials involving adults with PAH did not suggest any effect of age and weight on the pharmacokinetics of bosentan. However, there have been no studies to investigate the pharmacokinetics of bosentan in pediatric patients. Thus, it was necessary to examine the pharmacokinetic profiles in pediatric patients with PAH. Additionally, hemodynamic and exercise improvement data was obtained to evaluate the potential benefits of bosentan therapy in this patient population that would be referenced in the labeling.

The protocol for this study is entitled: “**AC-052-356 (BREATHE-3):** Pharmacokinetics and Tolerability of Tracleer™ (Bosentan) in Pediatric Patients with Pulmonary Arterial Hypertension: Single and Multiple Oral Doses (Study of Bosentan in Children with Pulmonary Arterial Hypertension) “

Reasons for Site Selection: There were two centers with a combined total of nineteen pediatric subjects enrolled in this study. According to the review division, Dr. Ivy’s results drove the efficacy results (i.e., findings for PVR). Dr. Ivy from Denver enrolled 10 patients and discontinued his study early. The rationale for selection of Dr. Ivy’s site was a high number of treatment responders and significant primary efficacy results pertinent to decision-making.

III. RESULTS (by site):

Name of CI, Address	Protocol # , Site #, and # of Subjects	Inspection Dates	Final Classification
Dunbar Ivy, M.D. Children's Hospital of Colorado 13123 E 16th Avenue B100 Aurora, CO 80045	AC-052-356 (BREATHE-3) Site #2 10 subjects	1/30/2017 – 2/23/2017	VAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Dunbar Ivy, M.D.
Children's Hospital of Colorado
13123 E. 16th Avenue B100
Aurora, CO 80045

The inspection of Dr. Dunbar Ivy was conducted between January 30, 2017 and February 23, 2017. Dr. Ivy has five IND studies in CDER's COMIS database and has no prior inspections.

The field investigator reviewed the following items during the inspection: informed consent and assent documents for each subject; IRB correspondence and approvals during the study; summary of site monitoring visits and monitoring correspondences; regulatory documents such as training records, delegation of responsibility logs and Notes to File; drug accountability records; visit schedules; subject binders for the ten enrolled subjects; progress notes; comparison of source records with data listings provided with the assignment for demographics, primary and secondary efficacy endpoints, other measured parameters, laboratory values, adverse events, protocol deviations.

A multi-item, 9 observational FDA-483 was issued to Dr. Ivy at the close of this inspection. The FDA-483 listed regulatory violations relating to:

1. Ensuring an investigation is conducted in accordance with the investigational plan;
2. Maintaining accurate and adequate case histories with respect to observations and other data pertinent to the investigation; and
3. Promptly reporting all changes in research activity to the IRB.

Dr. Ivy provided a written response to the FDA- 483, in a letter dated March 13, 2017. His response comprehensively addressed each item on the FDA 483, provided a root-cause analysis of why the observation occurred, and provided a well-crafted corrective action plan that he had implemented or intended to implement in the future.

Please note that each item listed on the FDA-483 was carefully reviewed and evaluated for its impact on efficacy and subject safety in order to arrive at our recommendation on data acceptability. Only observations cited on the FDA 483 which were considered significant regulatory violations are included, and in some cases, only examples of similar, multiple violations are included. This Clinical Inspection Summary (CIS) highlights observations noted during the inspection that we considered to adequately represent each violation, and does not include those observational items that were not considered to be regulatory violations. Post-inspectional correspondence from Dr. Ivy addressed each item listed on the FDA 483. The following regulatory violations were observed.

Observation 1: An investigation was not conducted according to the signed statement of investigator and investigational plan (21 CFR 312.60).

1. Subjects were enrolled for this study who did not meet inclusion and exclusion criteria.
 - a. Subject (b) (6): Viral serology laboratory tests necessary to exclude positive results for HIV, hepatitis B, and Hepatitis C were not collected during Visit 1 (Screening). The subject received study drug on 10/25/2001. These laboratory tests were collected 1/23/2002 at the Week 12 Visit (Final Visit).

Reviewer Comments: Results were reported negative on 1/28/2002. This was a protocol violation but unlikely to significantly impact the data results.

- b. Subject (b) (6): laboratory tests to screen for evidence of drugs of abuse (cocaine, tetrahydrocannabinol, opiates, and benzodiazepines) were not collected during Visit 1 (Screening) on 10/30/2001. The subject received study drug on 11/1/01. These tests were collected on 1/30/2002, three months late.

Reviewer Comments: This subject was five and unlikely to have had a history of drug use with these exclusionary drugs. This was a protocol violation but unlikely to significantly impact the data results

- c. Subject (b) (6): Cardiac catheterization performed on (b) (6) (Visit 2) reported cardiac index measurements of 1.73 L/min/m² and 2.16 L/min/m². Protocol section 3.3.2 (Exclusion Criteria) specifics that subjects will not be

included if cardiac index < 2 L/min/m² at the screening visit and/or prior to study medication initiation.

Reviewer Comments: The measurement of 2.16 L/min/m² was within normal limits, and this value was the official test result according to the PI. This issue is minor and unlikely to significantly impact the data results.

2. Subject (b) (6) was enrolled, but the subject expressed an oral aversion from prolonged intubation and therefore received medications in oral solutions and/or by gastrostomy tube. The study was to look at the safety and tolerance of a new **oral** experimental drug to treat PAH.

Reviewer Comments: Review of a communication obtained during the inspection from the sponsor dated February 21, 2017 documents that the sponsor permitted the site to continue to crush the study drug and administer the study drug via G-tube, for this subject. The response by the clinical investigator states that crushing and making a suspension could be considered an appropriate method of administration to reliably characterize bosentan PK. Although, the study was to look at the safety and tolerance of a new oral experimental drug to treat PAH, the above finding was isolated in nature and does not appear to affect the reliability of safety and efficacy data.

3. Subject (b) (6) Labs collected at Visit 2 (9/12/2001) documented an ALT value three times the upper limit of normal at 63 U/L (reference range 5-20 U/L). The subject received an initial dose of study drug on 09/13/2001. Laboratory findings were reported on 09/15/2001, but were not documented as reviewed by Dr. Ivy until 09/27/2001. Repeat ALT, collected on 09/19/2001 was reported on 9/21/2001 with an ALT of 27 UL, and were signed by Dr. Ivy on 9/26/2001 and noted as not clinically significant. Correspondence from the sponsor, dated 09/18/01, informed the site to stop the medication and retest every two weeks. However, study medication was not stopped during this time period. Unscheduled labs collected on 10/16/2001 reported the ALT as 18 U/L with a notation that the ALT level had returned to the normal reference range. Repeat ALT performed on 10/16/2001 was normal.

Reviewer Comments: This represents a protocol violation for not adhering to the sponsor's request to stopping the study drug for abnormal ALT levels. The protocol required that patients not be included in the study if at the screening visit and/or prior to the study medication initiation, AST and/or ALT values are $> 2X$ ULN. Furthermore, Amendment 2 of the protocol states that subjects with abnormal liver function tests (ALT/AST between 3-5 ULN) and without liver disease symptoms who have received the initial dose of study drug should stop bosentan therapy and be retested every 2 weeks until liver enzyme values return to baseline. In his response letter, Dr. Ivy acknowledged this may have posed a safety risk to the subject, and provided a corrective action plan and completed GCP training.

4. Screening labs collected for Subject (b) (6) on 7/19/2001 reported abnormalities for neutrophils, lymphocytes, monocytes, creatinine, AST and ALT. All were documented as not clinically significant and signed by Dr. Ivy on 8/5/2001. Lab values

for AST were reported as 53 U/L and for ALT as 42 U/L. Dr. Ivy documented that with the note that the report of these lab values as "screening labs within 2x ULN.... Will enroll in Breathe 3 trial." Subject (b) (6) had blood collected at Visit 2 on 07/25/2001 and was found to have an ALT value three times the upper limit of normal at 75 U/L (reference range 05-20 U/L). Laboratory results were reported on 07/26/2001, and state "printed 07/27/2001". The subject was administered the initial dose of study drug on 07/26/2001. Repeat testing of blood collected on 07/30/2001 yielded values of ALT 109 U/L (5 times the upper limit of normal), and AST of 74 U/L (reference range 10-40 U/L). Laboratory reports were documented as reviewed by Dr. Ivy on 08/7/2001, and the laboratory values were evaluated as clinically significant. The subject was not notified to stop bosentan therapy immediately as per the Protocol; the drug was stopped on 08/01/2001.

Reviewer Comments: Amendment 2 of the protocol states that subjects with abnormal liver function tests (ALT/AST between 3-5X ULN) and without liver disease symptoms who have received the initial dose of the study drug should stop bosentan therapy; be retested immediately to confirm results and retested every 2 weeks until live enzyme values return to baseline. Per protocol, study drug should have been held from July 26, 2001 (earliest known date when the CI became aware of abnormal LFT values). Although a notation indicates that the sponsor permitted the subject to continue on study with repeat laboratory studies on July 27, 2001 [the next day], the repeat labs were invalid due to hemolysis and were not repeated until July 30, 2001.

5. No electrocardiograms (ECGs) were performed for Subjects (b) (6) at the End of Treatment (EOT) visits.

Reviewer's Comments: This reflects a protocol violation for Subjects (b) (6) since both subjects did not have an ECG performed at their EOT visits on January 9, 2002 and January 14, 2002, respectively. However, on January 7, 2002, the sponsor permitted the site to allow the previous study visits to function as the EOT visit. According to the Table 1 Schedule of Assessments, an ECG was required to be performed at Screening, Visit 2, and Visit 5. No ECG was required at the Week 3 and 4 visit. Therefore, this finding is unlikely to significantly impact the outcome of the study.

6. The Borg dyspnea index was not completed for Subject (b) (6) during testing performed on 10/24/01 and 1/22/02.

Reviewer Comments: This represents a protocol violation but is an isolated finding and is not likely to significantly impact the outcome of the study because this was only one of several parameters measured as part of the secondary objectives for this study.

7. Records were not always maintained to document meals consumed, with prohibited beverages or food items (xanthine containing), according to Protocol Section 7.0, within 24 hours before the administration of study medication through the end of pharmacokinetic assessments performed at Visit 2 and Visit 5. In addition, these records fail to provide evidence of appropriate review. Examples include:

- Subject (b) (6) – only had a record of food intake for one day 05/23/2001 (PK collection).
- Subject (b) (6) – no source record existed of food intake in association with PK day 11/1/2001.
- Subject (b) (6) – food intake documents consumed caffeinated beverage on PK date 05/17/2001.
- Subject (b) (6) – documented intake of two thirds of a packet of M&M's on PK day 7/26/2001.

Reviewer's notes: Protocol Section 7.3 discusses dietary restrictions of caffeine and chocolate. Source records documented that Subject (b) (6) consumed caffeinated beverage and Subject (b) (6) consumed two-thirds packet of M&M chocolates on PK days 5/17/2001 and 7/26/2001, respectively. For Subjects (b) (6) and (b) (6), who had minimal or no entry for food intake on the days of their PK assessments, the protocol did not specifically require the use of a food diary or requirement to log dietary intake. These findings are minor and isolated and unlikely to have a significant impact on the study outcome.

Observation 2. The investigator shall promptly report to the IRB all changes in the research activity (21 CFR 312.66).

The site was forwarded Protocol Amendment 2 (dated 18 May 2001) by email on 05/22/2001. The amendment included changes towards a stricter guideline for abnormal liver function tests. The amendment and amended consents were forwarded to the IRB in December 2001, and approved on 12/16/2001.

Reviewer Comments: The site received Protocol Amendment 2 dated May 18, 2001 on May 22, 2001. This was not submitted to the IRB until December 2001. The regulations require that all changes in research activity must be sent to the IRB. Six subjects signed informed consent between June 7, 2001 and October 29, 2001. All subjects signed the Informed Consent Document that was dated April 25, 2001. This amendment, which included stricter language on guidelines for abnormal liver function, was submitted approximately 6 months after the site received the amendment. There does not appear to be any significant impact on data integrity or subject safety as the protocol already had guidelines for repeat laboratory studies and stopping rules for abnormal liver function, and the protocol amendment was ultimately submitted and approved.

Observation 3: An investigator is required to maintain accurate and adequate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug [21 CFR 312.62(b)]

The field investigator noted that some non-serious adverse events were not reported. For example:

- a. Subject (b) (6) experienced a mild headache on 6/13/2001 following the

administration of study drug, and was given Tylenol. No adverse event was reported.

- b. For Subject (b) (6) source records document the subject was administered 650 mg Tylenol at 13:50 on 8/16/2001, following dosing with 125 mg of study drug during the PK blood collections without further explanation. No adverse event was reported.
- c. For Subject (b) (6) source records document complaints of headache following the administration of the initial dose of study drug on 5/23/2001, at 0829. Tylenol (500 mg) was administered at 0900. Source records also document that flushing was observed on the face and left arm, and rash was noted on the legs. Complaints of the headache continued, and the subject was once again administered 500 mg of Tylenol at 1230. Although the headache was noted to be resolved on 5/23/2001, the rash was noted as present on 05/24/2001. These adverse events were not documented in the data listings.

Other minor discrepancies were found between source records and the data listings with respect to lab values for hemoglobin, hematocrit, bilirubin, neutrophils, AST, and ALT collected for Subject (b) (6) at Visit 4 on 8/8/2001; date that an ECG evaluation was performed for Subject (b) (6) at the EOT visit; blood pressure measurements for Subject (b) (6) at Visit 2, and bicycle ergometry values obtained for Subject (b) (6) on 10/22/2001 and Subject (b) (6) on 5/21/2001. These discrepancies were minor and unlikely to significantly impact data integrity.

{See appended electronic signature page}

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CC:

Central Doc. Rm. # NDA 209279
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/s/

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05/11/2017

SUSAN D THOMPSON
05/11/2017

KASSA AYALEW
05/11/2017

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: April 27, 2017

To: Norman Stockbridge, MD
Director
Division of Cardiovascular and Renal Products (DCaRP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Puja Shah, Pharm.D., RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): Tracleer (bosentan)

Dosage Form and Route: dispersible tablets, for oral use

Application Type/Number: NDA 209279

Applicant: Actelion Pharmaceuticals Ltd.

1 INTRODUCTION

On August 05, 2016, Actelion Pharmaceuticals, Ltd., submitted for the Agency's review an original New Drug Application (NDA) for Tracleer (bosentan) dispersible tablets, for oral use. Tracleer (bosentan) tablets, for oral use, is an endothelin receptor agonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. The purpose of the submission is to:

- provide for the use of Tracleer (bosentan) in the treatment of pediatric patients greater than 12 years of age with pulmonary arterial hypertension (PAH)
- provide for a new 32 mg dispersible tablet presentation
- incorporate the new Pregnancy and Lactation Labeling Rule (PLLR) labeling requirements into the previously approved label for Tracleer (bosentan).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Cardiovascular and Renal Products (DCaRP) on February 14, 2017, and August 23, 2016, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for Tracleer (bosentan) tablets, for oral use.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DCaRP under separate cover.

2 MATERIAL REVIEWED

- Draft Tracleer (bosentan) tablets, for oral use MG received on August 08, 2016, and received by DMPP and OPDP on April 19, 2017.
- Draft Tracleer (bosentan) tablets, for oral use Prescribing Information (PI) received on August 08, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on April 19, 2017, and OPDP on March 15, 2017.
- Approved Tracleer (bosentan) labeling dated October 20, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using

fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SHAWNA L HUTCHINS
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PUJA J SHAH
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BARBARA A FULLER
04/27/2017

LASHAWN M GRIFFITHS
04/27/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
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Division of Pediatric and Maternal Health Memorandum

Date: March 27, 2017 **Date Consulted:** Sept 26, 2016

From: Jane Liedtka M.D., Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Maryam Changi, PharmD, Regulatory Project Manager (RPM)
Division of Cardiovascular and Renal Products (DCRP)

Drug: Tracleer (bosentan) tablets

NDA: NDA 209279

Indication: Tracleer is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH) [World Health Organization (WHO) Group 1] to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with (b) (4) Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%)

Applicant: Actelion Pharmaceuticals Ltd

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- Applicant's background package for NDA 209279 submitted on August 5, 2016.
- Applicant's revised label, literature review and summary of pharmacovigilance database submitted as SD#12 on December 9, 2016.

Consult Question: PLLR updated labeling

INTRODUCTION

On September 26, 2016, DCRP consulted DPMH to provide input for appropriate format and content of the pregnancy and lactation sections of Tracleer (bosentan) tablet labeling to be in compliance with the Pregnancy and Lactation Labeling (PLLR) format.

REGULATORY HISTORY

- On August 5, 2016, Actelion Pharmaceuticals Ltd submitted a new NDA 209279 for Tracleer (bosentan) tablets.
- Tracleer (bosentan), an endothelin receptor antagonist (ERA) was originally approved in the U.S. under NDA 021290 on November 20, 2001 for the treatment of pulmonary arterial hypertension [World Health Organization (WHO) Group 1] to improve exercise ability and to decrease clinical worsening.
- The current submission is for a new formulation, a dispersible tablet, so it falls under a type 5 (New Formulation) NDA.
- On November 21, 2016, the Agency sent the Applicant an information request (IR) via email requesting that they submit a review and summary of the available published literature and a summary of the Applicant's pharmacovigilance database regarding Tracleer (bosentan) use in pregnant and lactating women.
- On December 9, 2016, the Applicant submitted the revised labeling and the requested supporting information which was adequate.

BACKGROUND

Bosentan and Drug Characteristics¹

- Available as 62.5 mg and 125 mg film-coated tablets for oral administration
- An endothelin receptor antagonist (ERA) that belongs to a class of highly substituted pyrimidine derivatives, with no chiral centers
- A specific and competitive antagonist at endothelin receptor types ETA and ETB
- Endothelin-1 (ET-1) is a neurohormone, the effects of which are mediated by binding to ETA and ETB receptors in the endothelium and vascular smooth muscle. ET-1 concentrations are elevated in plasma and lung tissue of patients with pulmonary arterial hypertension, suggesting a pathogenic role for ET-1 in this disease
- The terminal elimination half-life of bosentan is about 5 hours in healthy adult subjects.
- Bosentan has three metabolites, one of which is pharmacologically active and may contribute 10%–20% of the effect of bosentan.
- 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.

¹Tracleer (NDA 21290) package insert

- The absolute bioavailability of bosentan in normal volunteers is about 50% and is unaffected by food.
- Bosentan is highly bound (> 98%) to plasma proteins, mainly albumin.
- Bosentan has a molecular weight of $\approx$ ^{(b) (4)} Daltons.
- Common adverse reactions ($\geq 3\%$ more than placebo) observed in Tracleer clinical trials were respiratory tract infection and anemia.

Current State of the Labeling¹

- Current labeling for Tracleer (NDA 21290) was approved on October 20, 2016
- In the Physician Labeling Rule (PLR) format but does not comply with PLLR requirements
- Boxed warnings for hepatotoxicity and embryo-fetal toxicity
- Warnings and Precautions for avoiding use in pre-existing hepatic impairment, fluid retention, pulmonary veno-occlusive disease (consider discontinuing Tracleer if this occurs) and for decreased sperm counts
- Significant interactions with hormonal contraceptives are noted in the 2016 label. An interaction study demonstrated that co-administration of bosentan and a combination oral hormonal contraceptive produced average decreases of norethindrone and ethinyl estradiol levels of 14% and 31%, respectively. However, decreases in exposure were as much as 56% and 66%, respectively, in individual subjects.
- A restricted distribution program is in place for monitoring Tracleer use (Tracleer REMS Program) because of the risks of hepatotoxicity and embryo-fetal toxicity.
- There is a contraindication for pregnancy. Tracleer is categorized as “Pregnancy Category X” in the currently approved label. The prescriber should not dispense a prescription for Tracleer without documenting a negative urine or serum pregnancy test performed during the first 5 days of a normal menstrual period and at least 11 days after the last unprotected act of sexual intercourse. Monthly pregnancy testing is required during treatment. Patients may choose one highly effective form of contraception (intrauterine devices (IUD) or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner’s vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method.
- Effective contraception must be used during and for one month after Tracleer use. If Tracleer is used during pregnancy or if a patient becomes pregnant while taking Tracleer, the patient should be apprised of the potential hazard to the fetus.
- Section 8.3 Nursing Mothers states
It is not known whether bosentan is excreted into human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from bosentan, a decision should be made to discontinue nursing or to discontinue Tracleer, taking into account the importance of Tracleer to the mother.

Pulmonary Arterial Hypertension (PAH) and Pregnancy

In patients with PAH, pregnancy is associated with substantial morbidity and mortality, translating into a significant maternal and fetal risk². Patients with PAH usually deteriorate in the second trimester of pregnancy. Pregnancies resulting in delivery occur rarely in women with PAH, as illustrated by results from a large US health survey reporting only 182 deliveries in patients with idiopathic PAH (IPAH) out of an estimated 11.2 million deliveries between 2002 and 2004³. As described in the current *Guidelines for the diagnosis and treatment of pulmonary hypertension*, pregnancy is associated with a very high risk to mother and fetus and should be discouraged. Should a PAH patient become pregnant, termination of the pregnancy should be discussed. Patients who choose to continue pregnancy should be treated with disease-targeted therapies, and elective delivery should be planned.

A systemic review of all published reports from 1997 to 2007 found that overall maternal mortality was 17% in women with IPAH, 28% in PAH associated with congenital heart disease⁴ and 33% in PAH of other etiologies⁵. The causes of poor maternal outcomes are varied and include risk of death from right heart failure and stroke from intracardiac shunting⁶. Furthermore, there is a high peri-/post-partum risk due to hemodynamic stress, bleeding complications and the use of general anesthesia, which can all lead to right heart failure^{4,7}. The most common risk to the fetus is death⁸. In a publication describing pregnancy outcomes in women with PAH, the outcomes were considered poor with high rates of pre-term deliveries ranging from 85 to 100% and fetal growth restriction in up to one-third of pregnancies⁹. The same publication, summarizing data from the Registry Of Pregnancy and Cardiac Disease (ROPAC) of the European Society of Cardiology, covering cases in Europe and Africa observed between 2008 and 2014, showed a high maternal mortality (4/7) in patients with IPAH, while pregnancy outcomes in pulmonary hypertension due to left heart disease (most often affecting the mitral valve) appeared more favorable (3 maternal death cases in 112 pregnancies).

² Madden BP. Pulmonary Hypertension and Pregnancy. *Int J Obstet Anesth.* 2009; 18(2):156-164.

³ Chakravarty EF *et al.* Pregnancy outcomes in systemic sclerosis, primary pulmonary hypertension, and sickle cell disease. *Obstet Gynecol.* 2008; 111(4): 927–934 2008.

⁴ Weiss BM *et al.* Outcome of pulmonary Vascular Disease in pregnancy: A Systematic Overview from 1978 through 1996. *J Am Coll Cardiol.* 1998; 31(7): 1650-1657.

⁵ Bedard E *et al.* Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? *Eur Heart J.* 2009; 30(3):256–65.

⁶ Hsu CH *et al.* The management of pregnancy and pregnancy-related medical conditions in pulmonary arterial hypertension patients. *Int J Clin Pract Suppl* 2011; 175: 6–14.

⁷ Jais X *et al.* Pregnancy outcomes in pulmonary arterial hypertension in the modern management era. *Eur Respir J* 2012; 40: 881–885.

⁸ Gleicher N *et al.* Eisenmenger's syndrome and pregnancy. *Obstet Gynecol Surv* 1979; 34: 721–741.

⁹ Sliwa K *et al.* ROPAC investigators. Pulmonary hypertension and pregnancy outcomes: data from the Registry of Pregnancy and Cardiac Disease (ROPAC) of the European Society of Cardiology. *Eur J Heart Fail.* 2016; 18(9):1119–28.

Pregnancy and Lactation Labeling

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”¹⁰ also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule¹¹ format to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW

Pregnancy

Nonclinical Experience

In animal reproduction studies, oral administration of bosentan to pregnant rats at 2-times the maximum recommended human dose (MRHD) on a mg/m² basis caused teratogenic effects in rats, including malformations of the head, mouth, face, and large blood vessels.

For further details, the reader is directed to the Nonclinical Review by John Koerner, PhD.

Applicant’s Review of Literature

The Applicant submitted case reports regarding bosentan use in pregnancy retrieved from the scientific literature covering the period September 28, 1993 (international birth date) to August 19, 2016. The applicant did not give any more specific information regarding the parameters of their literature search. Twenty publications were cited. See Table 1 under “DPMH’s Review of the Literature” for details of the relevant articles.

DPMH’s Review of Literature

DPMH conducted a search of published literature in PubMed and Embase using the search terms “bosentan and pregnancy,” “bosentan and pregnant women,” “bosentan and pregnancy and birth defects,” “bosentan and pregnancy and congenital malformations,” “bosentan and pregnancy and stillbirth,” “bosentan and spontaneous abortion” and “bosentan and pregnancy and miscarriage.”

The notation regarding bosentan in Micromedex was its rating as a “category X” by the FDA.

¹⁰ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

¹¹ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

No reports of adequate and well-controlled studies of bosentan use in pregnant women were found. The details of relevant articles are in Table 1 below.

Table 1: Pregnancies Exposed to Bosentan Reported in the Published Literature

Pregnancy # Author/Year	Maternal Age	Diagnosis	Timing of Exposure	Outcome
#1 Doherty S <i>et al</i> ¹² 2003	21	Primary Pulmonary Hypertension (PAH)	Started at 35 weeks	Delivered vaginally at 39 weeks Healthy 8 lb baby girl-was “doing well” at 3 months
#2 Elliot <i>et al</i> ¹³ 2005	23	Iodiopathic Pulmonary Arterial Hypertension (IPAH)	Conception to week 6	Maternal cardiopulmonary arrest at 25 weeks, Cesarean section (C-section) delivery at 26 weeks, 0.65 kg male infant with APGARs of 8 + 9 at 1 and 5 minutes who required ventilation and neonatal intensive care unit (NICU), 16 months later- infant is “progressing well”
#3 Molelekwa V <i>et al</i> ¹⁴ 2005	23	Eisenmenger’s Syndrome*	Exposed throughout pregnancy	Scan at 30 weeks revealed intrauterine growth retardation (IUGR) and reduced fetal movement, planned cesarean section delivery of a 1.41 kg “healthy baby girl” who was in the NICU for 11 weeks with “good outcome” but “succumbed to respiratory syncytial virus (RSV) at 26 weeks post-partum”, No congenital malformations (CM) were noted
#4, #5 Kiely DG <i>et al</i> ¹⁵ 2010	23	IPAH	Conception to week 6	Delivery via C-section at 26 weeks of a 0.65 kg infant with APGARs of 8 + 9 at 1 and 5 minutes , No CM noted
	23	IPAH	Conception to week 9	Delivery via C-section at 34 weeks of a 1.58 kg infant with APGARs of 9 + 9 at 1 and 5 minutes , No CM noted, Maternal death at 4 weeks post-partum after patient discontinued her medications
#6 Streit M <i>et al</i> ¹⁶ 2009	29	Systemic Lupus Erythematosus (SLE)-PAH	Conception to week 5	Delivery via C-section at 37 weeks of a 2760 gm female infant with APGARs of 8 + 9 at 1 and 5 minutes , No CM noted

¹² Doherty S *et al*. Severe Primary Pulmonary Hypertension in Late Pregnancy Successfully Managed with the Endothelin Antagonist, Bosentan. Presented at the World Health Organization Pulmonary Hypertension Meeting, Venice Italy. 2003.

¹³ Elliot *et al*. The use of iloprost in early pregnancy in patients with pulmonary arterial hypertension. *Eur Respir J*, 2005. 26(1): p. 168-73.

¹⁴ Molelekwa V *et al*. Eisenmenger's Syndrome in a 27 Week Pregnancy - Management with Bosentan and Sildenafil. *Ir Med J*. 2005 March; 98 (3): 87-88.

¹⁵ Kiely DG *et al*. Improved survival in pregnancy and pulmonary hypertension using a multi-professional approach. *BJOG* 2010;117:565–574.

¹⁶ Streit M *et al*. Successful pregnancy in pulmonary arterial hypertension associated with systemic lupus erythematosus: a case report. *Journal of Medical Case Reports* 2009, 3:7255.

#7 Cotrim C <i>et al</i> ¹⁷ 2010	36	PAH-Not otherwise specified (NOS)	Started at 28 weeks	Emergency C-section at 29 weeks for severe worsening of maternal status and premature rupture of membranes, infant in NICU- no other infant information reported.
#8 Alvarez PA <i>et al</i> ¹⁸	28	Leflunomide- Induced PAH	Conception to week 12	None reported
#9 Smith JS <i>et al</i> ¹⁹ 2012	37	IPAH	Conception to week 4	Delivery via C-section at 36 weeks, No infant information reported.
#10 Sahni S <i>et al</i> ²⁰	23	Eisenmenger's Syndrome*	At diagnosis of pregnancy, NOS	Delivery via C-section at unknown EGA, No infant information reported.
#1 Picard <i>et al</i> . ²¹ 2015	22	SLE-PAH	Conception to week 5	Delivery via C-section at 32 weeks, reported that the baby grows No infant information reported.

*Eisenmenger's Syndrome: pulmonary hypertension at systemic level due to high pulmonary vascular resistance with reversed or bi-directional shunt through any large systemic to pulmonary communications [Ventricular-septal defect (VSD) was present in the case originally described]

Source: Reviewer's Table

Pharmacovigilance Database Summary

According to the Applicant,

Cumulatively from 28 September 1993 to 19 November 2015, Actelion GDS has received 228 confirmed reports of pregnancies occurring in 212 women on bosentan. Of the 228 confirmed reports, 43 cases were reported within the REMS program and 185 pregnancy reports worldwide outside of the REMS program. Sixty two (62) of the 185 pregnancies were reported in the US prior to the implementation of the REMS program. In addition to the 228 pregnancy reports in female PAH patients, 18 additional cases concern partners of 15 male patients who were treated with Tracleer.

Nineteen of the 228 reports can be excluded from this analysis: 10 patients had discontinued Tracleer for some time prior to conception or conceived more than 4 weeks after discontinuing Tracleer, 9 reports were of accidental exposure while preparing Tracleer for a patient.

With regard to exposure, of the remaining 209 reports:

¹⁷ Cotrim C *et al*. Three cases of pregnancy in patients with severe pulmonary arterial hypertension: experience of a single unit. *Rev Port Cardiol* 2010; 29 (01): 95-103.

¹⁸ Alvarez PA *et al*. Leflunomide-Induced Pulmonary Hypertension in a Young Woman with Rheumatoid Arthritis: A Case Report. *Cardiovasc Toxicol* (2012) 12:180–183.

¹⁹ Smith JS *et al*. Pulmonary Arterial Hypertension in the Setting of Pregnancy: A Case Series and Standard Treatment Approach. *Lung* (2012) 190:155–160.

²⁰ Sahni S *et al*. Pregnancy and pulmonary arterial hypertension: A clinical conundrum. *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health* 5 (2015) 157–164.

²¹ Picard *et al*. A complicated pregnancy (in French) *La Lettre du Pneumologue* Volume XVII, Septembre-October 2015. Translation provided by the applicant.

- o 172 pregnancies involved exposure to Tracleer in the first trimester of pregnancy only.
- o 10 involved exposure in the first and second trimesters.
- o 5 involved exposure to Tracleer throughout pregnancy.
- o 2 women started taking Tracleer at 22 weeks' gestation; one delivered a baby with a small patent foramen ovale (PFO), the other started Tracleer at 22 weeks in order to improve her PAH status sufficiently to be able to undergo a therapeutic abortion.
- o 1 woman was diagnosed with PAH and started Tracleer at 27 weeks' gestation and delivered a premature baby (normal development).
- o 1 woman received Tracleer only after the thirty-seventh week of gestation and delivered a normal baby.
- o 18 reports had insufficient information provided to assess time of exposure.

With regard to outcomes, because of the high risk associated with pregnancy for women with severe underlying PAH disease, or the unknown risk of teratogenicity, or both, induced abortions were performed in 83 of the 228 pregnancies [67/185 (36%) worldwide and 16/43 (37%) within the US REMS program].

The outcome of the remainder of 145 pregnancies includes:

- 35 spontaneous abortions (including 5 missed abortions and one abortion from a twin pregnancy, the other twin was a premature live birth)
- 6 abortions (not further specified)
- 3 ectopic pregnancies.
- 16 cases wherein the pregnancy was ongoing at the time it was reported
- 18 cases that were lost to follow-up
- 5 reports where the mother died (from pulmonary embolus, worsening of idiopathic pulmonary arterial hypertension (IPAH) and sepsis, worsening of PAH; right heart failure; the cause of death in the fifth case was reported as unknown)
- 2 fetal deaths [one was a stillbirth that occurred at 29 weeks following placental insufficiency due to maternal disease and resulting in intrauterine growth restriction (IUGR) (b)(6)] and the other was a premature birth by caesarean section at 24 weeks due to premature separation of the placenta (b)(6); the baby died of multiple organ failure due to extreme prematurity and it was not reported if there was a malformation]
- 60 live births
 - o 18 normal term babies,
 - o 2 normal babies (gestation not reported),
 - o 31 normal premature babies (no abnormalities reported),
 - o 3 premature births with malformations,
 - o a dichorionic, diamniotic twin pregnancy (with an outcome of one premature live birth and one spontaneous abortion) and
 - o 6 live births with various non-teratogenic disorders at birth

Details of the 3 premature births with malformations are as follows:

1. Case (b) (6): A female patient with IPAH with no other relevant medical history started Tracleer therapy at Week 22 and continued throughout the second and third trimesters. The baby was delivered at 35 weeks and developed neonatal respiratory distress syndrome and elevated bilirubin with jaundice which resolved with treatment. An echocardiogram at age of 8 days showed normal cardiac structure except for a small PFO with a left to right flow.
2. Case (b) (6): Tracleer exposure was in the first trimester and a male baby was delivered at 28.5 weeks gestation by Caesarean section. An initial echocardiogram revealed a patent ductus arteriosus (PDA) and a ventricular septal defect (VSD). The PDA was treated with indomethacin but later required surgical ligation, and a repeat echocardiogram revealed no VSD. A chromosome analysis after birth was normal although the baby developed multiple medical issues associated with a premature birth. Eight months after birth, the baby was reported as doing fine. Mother's medical history included an uncorrected VSD with Eisenmenger's physiology.
3. Case (b) (6): Tracleer exposure was in the first trimester. Cleft lip and cleft palate and 2 vessel umbilical cord were diagnosed by ultrasound at 20 weeks' gestation. The baby was delivered prematurely at 33 weeks. Paternal family history included cleft lip and palate.

Details of the 6 live births with other disorders are as follows:

1. Case (b) (6): Tracleer exposure was throughout pregnancy. The baby was delivered prematurely by caesarean section at 32 weeks' gestation, developed recurrent respiratory tract infections and chronic lung disease due to prematurity and eventually died at age 5 months of respiratory syncytial viral infection. Mother had PAH and Eisenmenger's.
2. Case (b) (6): Tracleer exposure was throughout pregnancy and baby was a normal delivery at 38 weeks. Baby was noted to have normal development with normal echography and karyotype at 19 weeks gestation, although bilateral pyelectasis was observed at prenatal echography which resolved after birth. Mother had PAH secondary to CREST syndrome.
3. Case (b) (6): Mother was accidentally exposed to Tracleer while preparing the drug for administration to her child with PAH (crushing and mixing tablets without using a mask or gloves) up to 32 weeks' gestation. Mother delivered a normal baby by caesarean section at term but with congenital hydronephrosis. Baby remained well at 6 months of age.
4. Case (b) (6): Tracleer had been stopped at 2 weeks gestation and pregnancy was discovered at 15 weeks gestation. IUGR was noted since 27th week of pregnancy and baby was delivered prematurely by caesarean section at 35 weeks due to fetal distress; baby developed neonatal respiratory distress and episodes of hypoglycemia which eventually resolved. Otherwise baby had normal development. Mother was on Tracleer for scleroderma.

5. Case (b) (6): Tracleer exposure was in the first trimester. Baby was delivered prematurely by caesarean section at 33 weeks gestation with intrauterine growth retardation and retinopathy of prematurity. Mother had PAH and Eisenmenger's syndrome.
6. Case (b) (6): Tracleer exposure was prior to conception. Baby was delivered prematurely with respiratory distress at 32 weeks gestation; Baby was healthy at 6 months of age.

According to the Applicant,

Tracleer has been shown to be teratogenic in rats at plasma levels 1.5 times the plasma concentrations achieved at the therapeutic dose in humans. Teratogenic effects included malformations of the head and face and of the major vessels, and were dose-dependent. The similarities of the pattern of malformations observed with other endothelin (ET) receptor antagonists and in ET knock-out mice indicate a class effect. However, extrapolating toxicological manifestations in animals to adverse reactions in humans has been shown to have a poor correlation.

There is still minimal data on the use of Tracleer in pregnant women...209 reports of new pregnancies while on Tracleer therapy have been reported worldwide...Of the 60 live births, 51 were reported as normal babies, including 3 babies whose mothers continued Tracleer therapy throughout pregnancy. The number of premature deliveries (31/60) is expected in the management of pregnancy in this high-risk group of patients...There were 3 reports of malformations among the other live births...For the 6 live births with various non-teratogenic disorders, the medical complications can be attributed to fetal risks associated with the underlying maternal condition resulting in growth restriction and preterm delivery...the post-marketing reports of normal live births with a few who were exposed throughout pregnancy, and the isolated reports of malformation with alternative explanations do not show a consistency of the effect. The significance of Tracleer-induced teratogenicity in animal studies to humans remains unknown and this is reflected in the drug product labeling of Tracleer.

Reviewer's Comments

I agree with the Applicant that it is difficult to interpret the limited information available regarding Tracleer use in pregnant women.

Summary

Limited human pregnancy outcome data for bosentan were found in the published literature. There were a variety of outcomes reported after exposure during pregnancy from the applicant's pharmacovigilance database. The findings in animal studies demonstrated embryofetal toxicity at doses near the maximum human doses. The Applicant proposes a contraindication to use of bosentan in pregnancy. Since there is evidence of fetal risk based on mechanism of action and

animal studies, DPMH agrees and recommends that the bosentan is contraindicated in pregnancy.

Lactation

Nonclinical Experience

There is no nonclinical information regarding the presence of bosentan in human or animal milk.

Applicant's Review of Literature

The Applicant searched the scientific literature covering the period September 28, 1993 (international birth date) to August 19, 2016 using PubMed, Medline and Embase. The search for bosentan (as well as the respective Actelion compound numbers) in combination with terms relating to breast feeding and/or lactation was used. No relevant articles or case reports describing bosentan use in lactating women were retrieved.

DPMH Review of Literature

DPMH conducted a search of *Medications and Mother's Milk*²², the Drugs and Lactation Database (LactMed),²³ Micromedex²⁴, and of published literature in PubMed and Embase using the search terms "bosentan and lactation" and "bosentan and breastfeeding." No reports of adequate and well-controlled studies of bosentan use in lactating women were found.

In *Medications and Mother's Milk*²², the author notes that there is "No data" regarding bosentan and that it is "possibly hazardous" due to its 50% bioavailability and high incidence of liver toxicity.

Bosentan is referenced in LactMed²³. The summary of use during lactation states: "There is little published experience with bosentan during breastfeeding. An alternate drug may be preferred, especially while nursing a newborn or preterm infant".

Micromedex notes the following; "Infant risk cannot be ruled out".

Neonatal Exposure

²² Hale, Thomas (2012) *Medications and Mothers' Milk*. Amarillo, Texas Hale Publishing, pg. 422-423.

²³ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

²⁴ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 7/1/16.

There were two publications concerning the use of bosentan for the treatment of persistent pulmonary hypertension of the newborn (PPHN) which are summarized below:

- Mohamed WA and Ismail M²⁵ reported on a prospective, randomized, double-blind, placebo-controlled trial of bosentan for PPHN. There were 24 subjects who received bosentan which was superior to placebo (88% response vs 20%). There were no drug-related clinical or laboratory adverse events. The authors mentioned 4 previous case reports of use of bosentan in a neonate^{26,27,28}.
- Steinhorn RH, *et al*²⁹ reported on a randomized, double-blind, placebo-controlled trial of efficacy, safety and pharmacokinetics using bosentan as adjunctive therapy (in addition to inhaled nitric oxide) for PPHN. There were 21 neonates treated and bosentan was well tolerated, but did not improve oxygenation or other outcomes.

Summary

There are no data on the presence of bosentan in human or animal milk. Based on potential serious adverse events anticipated in infants exposed to bosentan, DMPH recommends that patients be advised not to breast feed while taking bosentan. This is the recommendation in the currently approved label.

Use in Females and Males of Reproductive Potential

Nonclinical Experience

The development of testicular tubular atrophy and impaired fertility has been linked with the chronic administration of certain endothelin receptor antagonists in rodents.

Treatment with bosentan at oral doses of up to 1500 mg/kg/day (50 times the MRHD on a mg/m² basis) or intravenous doses up to 40 mg/kg/day had no effects on sperm count, sperm motility, mating performance or fertility in male and female rats. An increased incidence of testicular tubular atrophy was observed in rats given bosentan orally at doses as low as 125 mg/kg/day (about 4 times the MRHD and the lowest doses tested) for two years but not at doses as high as 1500 mg/kg/day (about 50 times the MRHD) for 6 months. Effects on sperm count and motility were evaluated only in the much shorter duration fertility studies in which males had been exposed to the drug for 4-6 weeks. An increased incidence of tubular atrophy was not observed in mice treated for 2 years at doses up to 4500 mg/kg/day (about 75 times

²⁵ Mohamed WA and Ismail M. A randomized, double-blind, placebo-controlled, prospective study of bosentan for the treatment of persistent pulmonary hypertension of the newborn. *Journal of Perinatology* (2012) 32, 608–613.

²⁶ Nakwan N *et al*. Successful treatment of persistent pulmonary hypertension of the newborn with bosentan. *Acta Paediatr* 2009; 98: 1683–1685.

²⁷ Goissen C *et al*. Persistent pulmonary hypertension of the newborn with transposition of the great arteries: successful treatment with bosentan. *Eur J Pediatr* 2008; 167: 437–440.

²⁸ Radicioni M *et al*. Combination therapy for life-threatening pulmonary hypertension in a premature infant: first report on bosentan use. *Eur J Pediatr*. e-pub ahead of print 8 March 2011.

²⁹ Steinhorn RH, *et al*. Bosentan as Adjunctive Therapy for Persistent Pulmonary Hypertension of the Newborn: Results of the Randomized Multicenter Placebo- Controlled Exploratory Trial. *J Pediatr* 2016;177:90-6.

the MRHD) or in dogs treated up to 12 months at doses up to 500 mg/kg/day (about 50 times the MRHD).

For further details, the reader is directed to the Nonclinical Review by Haw-Jyh (Brian) Chiu, PhD.

Applicant's Review of Literature

A literature review for publications associated with the use of bosentan affecting reproductive potential in males or females, covering the period September 28, 1993 (international birth date) to August 19, 2016 within Embase®, Medline® and PubMed through 26 Jul 2016, revealed no relevant publications.

The Applicant's proposed label describes the following study that was performed to assess the effects of bosentan on male fertility:



DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed and Embase regarding bosentan and its effects on fertility and found no relevant articles regarding the topic of fertility in males and females of reproductive potential.

Summary

Animal reproductive studies of administration of bosentan did show adverse effects on fertility with "atrophy of the prostate and seminal vesicles" in rats and hypospermatogenesis and atrophy of the prostate and epididymides in dogs. There are human data available on the effect of bosentan on fertility that demonstrate an adverse effect (in this small study the effect appeared to be reversible). Based on human and animal fertility studies, bosentan may impair

fertility in male patients. Therefore, section 8.3 will also contain a section describing the potential for bosentan to impair male fertility.

CONCLUSIONS

Based on the literature review and review of the pharmacovigilance database, DPMH has the following recommendations for TRACLEER (bosentan) labeling:

- **Contraindications, Section 4**
 - The “Contraindication” section of TRACLEER (bosentan) labeling was revised.
- **Warnings and Precautions, Section 5.2**
 - The “Warnings and Precautions” section of TRACLEER (bosentan) labeling was updated to correspond with changes made to the HPI, FPI and sections 4.1, 5.2, 8.1, 8.2, 8.3 and 17 of labeling.
- **Pregnancy, Section 8.1**
 - The “Pregnancy” subsection of TRACLEER (bosentan) labeling was structured in the PLLR format to include the “Risk Summary” and “Data” sections.³⁰
- **Lactation, Section 8.2**
 - The “Lactation” subsection of TRACLEER (bosentan) labeling was formatted in the PLLR format to include the “Risk Summary” section.³¹
- **Females and Males of Reproductive Potential, Section 8.3**
 - The “Females and Males of Reproductive Potential” subsection of TRACLEER (bosentan) labeling was formatted in the PLLR format to include the “Infertility” section.³²

LABELING RECOMMENDATIONS

DPMH revised the HPI and sections 4, 5.2, 8.1, 8.2 and 8.3 and 17 of TRACLEER (bosentan) labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with DCRP on 2/14/17. DPMH refers to the final NDA action for final labeling.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

³⁰ *Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format*. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

³¹ *Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format*. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

³² *Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format*. December 2014. Part IV Specific Subsection C-8.3 Females and Males of Reproductive Potential.

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/s/

JANE E LIEDTKA
03/27/2017

LYNNE P YAO
03/30/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: March 20, 2017

To: Maryam Changi, Pharm.D.
Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCaRP)

From: Puja Shah, Pharm.D., RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Consult Response
NDA 209279
TRACLEER® (bosentan) tablets, for oral use

As requested in DCaRP's consult dated August 23, 2016, OPDP has reviewed the draft Package Insert (PI), Carton and Container Labeling (CCL), and Medication Guide (MG) for TRACLEER® (bosentan) tablets, for oral use (Tracleer). OPDP's comments are based on the substantially complete version of the labeling titled "Sponsor PI-PLR-PLLR labeling Track change NDA 209279.docx" which was accessed via <http://sharepoint.fda.gov/orgs/CDER-DCRP/Maryam%20Changi/Forms/AllItems.aspx?RootFolder=%2FForgs%2FCDER%2DDCRP%2FMaryam%20Changi%2FNDA%20209279%5F%20Bosentan&FolderCTID=0x01200002DFF6C641E92D4D913018FDE015B38D&View=%7b7F1B7165-8808-409E-9AC4-B215E5B777A2%7d> on March 15, 2017.

Package Insert and Medication Guide

Our comments on the draft PI and MG are included directly on the attached copy of the labeling.

Carton and Container Labeling

OPDP reviewed the following proposed CCL accessed on March 20, 2017:

- Draft Carton Label accessed via <\\cdsesub1\evsprod\nda209279\0000\m1\us\carton-926pp05.pdf>
- Draft Container Label accessed via <\\cdsesub1\evsprod\nda209279\0000\m1\us\blister-927pp05.pdf>

- Draft Safety Seal accessed via <\\cdsesub1\evsprod\nda209279\0000\m1\us\safety-seal-07000003-3.pdf>

OPDP does not have any comments on the proposed CCL at this time.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Puja Shah at 240-402-5040 or puja.shah@fda.hhs.gov

39 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

PUJA J SHAH
03/20/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 8, 2017
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 209279
Product Name and Strength:	Tracleer (bosentan) Tablet for Suspension, 32 mg
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Actelion Pharmaceuticals LTD
Submission Dates:	August 5, 2016, November 9, 2016, and November 18, 2016
OSE RCM #:	2016-1918
DMEPA Primary Reviewer:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

Actelion Pharmaceuticals LTD submitted container labels, carton labeling, prescribing information (PI), and the medication guide for Tracleer (Bosentan) tablet for suspension on August 5, 2016.

Tracleer (Bosentan) tablets, film-coated, were approved on November 20, 2001 under NDA 021290. Although the proposed Tracleer (Bosentan) tablet for suspension is submitted under NDA 209279, both NDA 021290 and NDA 209279 will be managed in a single PI.

Per the FDA reviewers' guide submitted on August 5, 2016, the purpose of the submission is described as follows:

- Provides for the use of Tracleer in the treatment of pediatric patients <12 years of age with pulmonary arterial hypertension (PAH).
- Provides for a new 32 mg dispersible tablet presentation of Tracleer, including the blister container label, carton labeling, and safety seal artwork for the proposed 56 dispersible tablet quantity (e.g., 14 dispersible tablets per blister card, with 4 blister cards per carton).
- Incorporates the new labeling requirements as related to the Pregnancy and Lactation Labeling Rule into the previously approved label for Tracleer.

Actelion Pharmaceuticals LTD then submitted an updated PI on November 9, 2016 which incorporated information from a Prior Approval Supplement approved by the Agency on October 20, 2016. The updates from the Prior Approval Supplement included changes to PI sections 4.4 (Hypersensitivity) and 6.2 (Postmarketing experience). Next, Actelion Pharmaceuticals LTD submitted another updated PI version on November 18, 2016 in response to the Agency's request for a tracked changes version that accepts the changes that are already in the approved labeling.

This review evaluates the proposed container labels, carton labeling, PI, and medication guide for Tracleer (Bosentan) for risk of medication error in response to a request from the Division of Cardiovascular and Renal Products (DCRP).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The newly proposed Tracleer 32 mg tablet for suspension and the pediatric dosing of (b) (4) require splitting the proposed tablet for suspension (b) (4)

Upon evaluation of the proposed Tracleer tablet for suspension, we noted several safety issues:

(b) (4)

2. Quadrisection on the tablet for suspension

The (b) (4) does not align with the Clinical Pharmacology recommended dosing of 16 mg, 32 mg, 48 mg, and 64 mg (e.g., ½ tablet, 1 tablet, 1.5 tablets, and 2 tablets, respectively). Specifically, the end-user would only need to split the tablet in half (b) (4) to achieve the aforementioned doses. Thus, the (b) (4) dosing has been revised to include a minimum dose of ½ tablet.

We defer to CMC on whether or not the (b) (4) is functional.

3. Blister Pack Packaging Does Not Allow for Storage of Leftover Tablet Pieces

Because the prescribed dose may require splitting the proposed Tracleer tablet for suspension, once a whole tablet is removed from the protective blister and broken into pieces, leftover pieces would need to be stored adequately until the next dose. The proposed PI does not include instructions on where to store the leftover pieces of the proposed Tracleer tablet for suspension. We recommend adding specific storage instructions for leftover pieces of Tracleer tablet for suspension to the PI, or reconfiguring your packaging from blister strip to bottle.

After evaluating the proposed container labels, carton labeling, PI, and Medication Guide, we note inconsistencies between the Medication Guide and the rest of labeling:

- Medication Guide states: "Tracleer 32 mg dispersible tablets contain Aspartame, Phenylketonurics: Contains Phenylalanine (b) (4) per 32 mg dispersible tablet."
- Container label, carton labeling, and PI: "Phenylketonurics: Contains Phenylalanine 1.87 mg per dispersible tablet."

We notified CMC of the inconsistency and deferred to them on the determination of the accuracy of the above statements, and we recommended consistently providing accurate information across all labels and labeling.

We also contacted CMC for their determination of the established name and dosage form on the labels and labeling. Per email communication received from CMC on January 18, 2017 (snapshot below), the established name is "(bosentan) tablets for suspension."

Location:	Current:	Correct:
Carton	(b) (4)	TRACLEER® (bosentan) Tablets for Suspension 32 mg
Perforated blister		TRACLEER® (bosentan) Tablets for Suspension 32 mg Also acceptable: TRACLEER® (bosentan) Tablets for Suspension 32 mg

In addition, the proposed administration instruction in the proposed PI just states to (b) (4). The proposed labels and labeling do not include an instruction for use (IFU) for the patient, but we do note administration instructions in the proposed Medication Guide.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed labels and labeling for Bosentan may be improved to promote the safe use of the product as described in Section 4.1 and Section 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI)

See Appendix H for the DMEPA's recommendations in tracked changes for the PI and Medication Guide.

4.2 RECOMMENDATIONS FOR ACTELION PHARMACEUTICALS LTD

We recommend the following be considered and/or implemented prior to approval of this NDA:

A. Medication Guide

1. Based on dosing for patients less than or equal to 12 years of age, the quantity dispensed may be less than a carton of 56 tablets for suspension. Ensure that enough copies of the medication guide are included in the carton so that all patients receive a copy of the medication guide.

B. Container Labels and Carton Labeling

1. Revise the presentation of the proprietary and established names, and the strength to read:^a

Tracleer (Bosentan) Tablets for Suspension 32 mg	or	Tracleer (Bosentan) Tablets for Suspension 32 mg
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2. Revise the strength presentation on the blister cell labels and carton labeling to describe the mg amount of drug per single blister unit, as follows: "32 mg per tablet for suspension." This may help prevent confusion about how much product is contained in a single blister unit as compared to the total contents of the entire blister card.^a
3. We note the same NDC number (66215-103-56) is present on the carton labeling and each unit-dose blister pack. The unit-dose blister label of 1 tablet for suspension and the carton labeling of 56 tablets for suspension should have different NDC numbers. Revise the NDC package code (last 2 digits) of the NDC numbers so that the unit-dose blister label and the carton labeling NDC numbers are different for these package configurations. In addition, ensure both NDC numbers are provided in Section 16 of the full PI. (See recommendation 4.2 C1.).

C. Container Labels

1. We recommend adding the barcode (with NDC number) and manufacturer to each perforated blister cell label so that this important information remains available to the end user up to the point at which the last dose is removed. To

^a Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

facilitate this, we recommend decreasing the size of the phrase on Phenylketonurics (“Phenylketonurics: Contains Phenylalanine at 1.87 mg per dispersible tablet.”). If space still does not allow for placement of the Phenylketonurics statement, barcode, and manufacturer to each blister cell label, a random display of this information can appear multiple times across the back of the blister or the important information should be displayed in such a manner that it is not destroyed or eliminated when dosage units are removed.^a

D. Carton Labeling

1. Relocate the statement “Attention: Dispense with enclosed Medication Guide.” to the principal display panel (PDP) in accordance with 21 CFR 208.24(d).
2. Add the additional storage information for the leftover pieces of tablets for suspension to the storage information provided on the carton labeling as follows: “Store at controlled room temperature 20°C – 25°C (68°F – 77°F). Store divided tablets for suspension at controlled room temperature 20°C – 25°C (68°F – 77°F), and use within 7 days.”
3. We recommend expanding upon the “Usual Dosage: See enclosed full prescribing instructions.” instructions on the carton labeling by adding the additional instructions related to preparation and administration of the tablet for suspension (e.g., (b) (4)).
4. We note the following phrase on the side panel of the carton labeling: “Important: Read accompanying directions carefully.” Clarify what is meant by “accompanying directions” (e.g., prescribing information, medication guide, etc.).
5. Revise the net quantity statement to read:
Contains: 56 tablets for suspension per carton.
Each carton contains 4 blister-strips of 14 tablets each.
Ensure the net quantity statement appears on the principal display panel (PDP) separate from and less prominent than the statement of strength.^a

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tracleer (Bosentan) that Actelion Pharmaceuticals LTD submitted on November 18, 2016. Proposed in grey highlights.

Table 2. Relevant Product Information for Tracleer (Bosentan)	
Initial Approval Date	Tracleer (Bosentan) originally approved on November 20, 2001 under NDA 021290; NDA 209279 not yet approved
Active Ingredient	Bosentan
Indication	Tracleer is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with (b) (4) Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%). Considerations for use: Consider whether benefits offset the risk of hepatotoxicity in WHO Class II patients. Early hepatotoxicity may preclude future use as disease progresses
Route of Administration	Oral
Dosage Form	Film-coated tablets Tablet for suspension
Strength	Film-coated tablets: 62.5 mg and 125 mg Tablet for suspension: 32 mg
Dose and Frequency	-Patients >12 years of age: initiate at 62.5 mg twice daily with or without food; for patients >40 kg, increase to 125 mg twice daily after 4 weeks -Patients ≤ 12 years of age: initial and maintenance dosage is (b) (4) twice daily, with or without food
How Supplied	62.5 mg film-coated tablets Bottle containing 60 tablets. Carton of 30 tablets in 10 blister strips of 3 tablets. 125 mg film-coated tablets Bottle containing 60 tablets. Carton of 30 tablets in 10 blister strips of 3 tablets. 32 mg tablets for suspension Carton of 56 tablets for suspension in 4 blister-strips of 14 tablets.
Storage	Store at 20°C – 25°C (68°F – 77°F). Excursions are permitted

	between 15°C and 30°C (59°F and 86°F). [See USP Controlled Room Temperature]. These storage temperatures apply to both film-coated and tablets (b) (4) Divided tablets (b) (4) should be stored under the same conditions and used within 7 days.
Container Closure	-62.5 and 125 mg film-coated tablets: packaged in white high-density polyethylene bottle and a white polypropylene child-resistant cap or in foil blister-strips for hospital unit-dosing - 32 mg tablet for suspension: packaged in child resistant Aluminum/Aluminum peel-push blisters

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On November 1, 2016, we searched the L:drive and AIMS using the terms, “Bosentan,” “Tracleer,” and NDA “209279” to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 2 previous reviews^{b,c} evaluating the blister pack container labels and carton labeling for Tracleer 62.5 mg and 125 mg tablets for hospital unit dosing. We confirmed that our previous recommendations were implemented or considered.

^bBrennan, C. Label and Labeling Review for Tracleer (NDA 021290/S-020). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 MARCH 24. RCM No.: 2011-36.

^cBrennan, C. Label and Labeling Review Memorandum for Tracleer (NDA 21290/S-020). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 JULY 15. RCM No.: 2011-36.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On November 1, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the labels and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Searched the Acute Care, Community, and Nursing Newsletters.
Search Strategy and Terms	Match Any of the Words: Tracleer Bosentan

D.2 Results

Our search retrieved 12 newsletters, of which 3 of the newsletters published from 2006 to 2007 describe the same medication error case potentially related to the Tracleer (Bosentan) tablet labels and labeling.^{d,e,f}

The medication error case described a pregnant nurse splitting a Tracleer (Bosentan) tablet for a pediatric patient and later learning that Tracleer falls into pregnancy category X. After contacting the manufacturer Actelion Pharmaceuticals (Actelion), Actelion stated:

“It is not recommended to crush the tablets before dissolving them. Exposure to dust from crushed Tracleer tablets should be avoided and appropriate precautions should be taken (e.g., mask and gloves). Women of child-bearing potential, in particular, should avoid exposure to the dust.”

ISMP stated that the prescribing information and medication guide for Tracleer do not contain special handling instructions for healthcare professionals or any warnings about crushing or splitting the tablets. ISMP believes that such special handling information should be included in the prescribing information so that institutions will be able to construct policies for the safety and protection of healthcare personnel. ISMP cites precedence with Proscar (Finasteride) labeling.

We communicated this teratogenicity concern described by ISMP to the Review Team. Per the February 14, 2017 meeting discussion, the Review Team concluded that the evidence on the association between skin exposure to Tracleer and teratogenicity is lacking, and so special handling instructions are not being considered at this time. We align with the Review Team on this teratogenicity issue.

^d Institute for Safe Medication Practices. Can't touch this! ISMP Med Saf Alert Acute Care. 2006;11(5): 3.

^e Institute for Safe Medication Practices. Pregnancy alert: Can't touch this! ISMP Med Saf Alert Nurse Advise-ERR. 2007;5(3): 4.

^f Institute for Safe Medication Practices. Category X drug Tracleer (bosentan). ISMP Med Saf Alert Acute Care. 2006;11(8): 6.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁸ we reviewed the following Tracleer (Bosentan) tablet for suspension labels and labeling submitted by Actelion Pharmaceuticals LTD on August 5, 2016 and November 18, 2016.

- Blistercard Container Label submitted on August 5, 2016
- Blistercard Carton Labeling submitted on August 5, 2016
- Prescribing Information submitted on November 18, 2016
- Medication Guide submitted on November 18, 2016

G.2 Label and Labeling Images

Blistercard Container Label



⁸ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

15 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

SARAH E THOMAS
03/08/2017

CHI-MING TU
03/08/2017

Memorandum (Pediatric Ethics Consultation)

To: Maryann Gordon, M.D. (CDER/OND/ODEI/DCRP)
Aliza Thompson, M.D. (CDER/OND/ODEI/DCRP)
Maryam Kord Bacheh Changi, Pharm.D. (CDER/OND/ODEI/DCRP)

From: Donna L. Snyder, M.D.
Medical Officer, Pediatric Ethics
Office of Pediatric Therapeutics, OC/OSMP/OPT

Through: Robert M. Nelson, M.D., Ph.D.
Senior Pediatric Ethicist/Acting Director
Office of Pediatric Therapeutics, OC/OSMP/OPT

Date: January 12, 2017

Subject: NDA 209279 – Bosentan (Tracleer)

MATERIALS REVIEWED:

1. Request for Ethics Consultation, July 22, 2015, IND 58317, DARRTS Reference ID: 3795840
2. OPT consult review regarding pulmonary vascular resistance index (PVRI) for studies in pulmonary artery hypertension (PAH) in Pediatrics, dated November 16, 2010
3. (b) (4)
4. Letter to Sponsor regarding right heart catheterization (RHC) as an outcome in studies, dated March 7, 2012, DARRTS Reference ID: 3098813
5. Internal Meeting Minutes to discuss pediatric development with the sponsor, dated June 22, 2012, DARTTS Reference ID: 3149680
6. Sponsor Background Meeting Package, submitted June 17, 2015, to discuss pediatric development
7. Filing Review Issues Identified (74-day) Letter, dated October 18, 2016, DARRTS Reference ID: 4000284
8. Sponsor Responses to FDA Day 74 Filing Letter, submitted on December 20, 2016
9. Summary Review, NDA 203109, Revatio (sildenafil citrate), dated May 15, 2012, DARRTS Reference ID: 3131055
10. Tracleer (bosentan) labeling from Drugs@FDA, accessed December 30, 2016, http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021290s033lbl.pdf

Published Literature

The reference list is included at the end of the consultation, following the recommendations.

BACKGROUND:

The Office of Pediatric Therapeutics (OPT) received a consultative request from the Division of Cardiovascular and Renal Products (DCRP) on July 22, 2015 to address ethical questions related to the use of data collected through right heart catheterization (RHC) as an outcome measure in pediatric studies. The Division provided the following background and proposed questions:

“Actelion study AC-052-356, in which Pulmonary Vascular Resistance (PVR) measured by Right Heart Catheterization (RHC) was conducted prior to 2002, will be the clinical data source for a pre-sNDA to add a

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pediatric indication to NDA 21290, Tracleer. We came to the conclusion that repeat RHCs for the purpose of a clinical study are unethical during the review for sildenafil pediatric supplement (2012). Please address the ethics of reliance upon study AC-052-356.”

Product Description and Regulatory History

Bosentan (Tracleer) is an orally administered endothelin receptor antagonist approved on November 20, 2001. The product is indicated in adults for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Bosentan was granted orphan designation on October 6, 2000 for treatment of PAH and consequently, requirements under the Pediatric Research Equity Act (PREA) do not apply. In the European Union, Bosentan is approved for use in pediatric patients 1 year of age and older for treatment of PAH based on studies agreed to in a Pediatric Investigation Plan (PIP). Although not bound by any regulatory requirement, the sponsor has submitted pediatric studies to support product labeling in the US, citing an unmet need in the pediatric population for treatment options for PAH.

(b) (4)

In parallel, the Cardioresenal Advisory Committee (CRAC) met on July 29, 2010 to discuss a correlative model of PVR and 6-minute walk distance (6MWD) to be used in pediatric studies (specifically studies of sildenafil) of Pulmonary Arterial Hypertension (PAH). Pediatric studies in PAH had stalled because the 6MWD could not be administered to younger children. Data from adult studies illustrated a consistent relationship between change in exercise capacity (6MWD) and PVRI. The Committee determined (vote 7 to 6) that PVRI could be used to bridge the adult indication to pediatric patients and that for products with an approved PAH indication in adults, a change in treatment effect of PVRI can be used to support efficacy in the pediatric population.

(b) (4)

OPT was consulted in November 2010 regarding whether the use of RHC to collect PVRI data was acceptable under 21 CFR Subpart D. OPT opined that unless the procedure offered a prospect of direct benefit to pediatric patients (21 CFR 50.52), the risk must be either minimal (21 CFR 50.51) or a minor increase over minimal risk (21 CFR 50.53). Procedures done for diagnostic purposes as standard of care offer prospect of direct benefit, and are approvable under 21 CFR 50.52; however, procedures that are done solely for research purposes do not. OPT noted that serious adverse events may occur with RHC, and that if done for research purposes, and in situations where there was no prospect of direct benefit, RHC is not approvable as a minor increase over minimal risk (21 CFR 50.53).

(b) (4)

In September 2011, the sponsor submitted a (b) (4) revised study plan that included the recommended changes (b) (4) from April 2011. This study proposed RHC as a study endpoint. DCRP issued a letter to the sponsor stating the following:

(b) (4)

The sponsor noted in a telecon discussion that studies would need to be completed by August 2014 in order to for the sponsor to be eligible for exclusivity. No subsequent discussions on a (b) (4) occurred with the sponsor after this letter was issued.

Pediatric Studies Submitted for Bosentan

The sponsor has submitted the following studies for review:

- AC-052-365 (FUTURE-1) – open-label, single arm, 12-week, PK (pharmacokinetic) and tolerability study in 36 pediatric patients 2 to 12 years of age. Study completed November 15, 2007. RHC done at baseline.
- AC-052-373 (FUTURE-3) – open-label, randomized, comparative (2-dose), parallel group, 24-week PK and tolerability study in 64 pediatric patients ages 3 months to 12 years of age. Study completed February 5, 2014. RHC done at baseline and in 10 patients at centers where repeating RHC is standard of care.
- AC-052-356 (BREATHE-3) – open-label, parallel-group, single and multi-dose, 12-week, PK and tolerability study in 19 pediatric patients 3 to 15 years of age. Study report completed on April 8, 2002. RHC done at baseline and at 12 weeks.
- AC-052-367 (FUTURE-2) – open-label long-term extension to FUTURE 1 in 36 pediatric patients. Median duration of patient participation was 119.9 weeks. Study report completed December 17, 2012. No RHC done as part of this study.
- AC-052-374 (FUTURE-3 extension) – open-label, long-term extension study of FUTURE 3 in 50 pediatric patients. Median cumulative patient exposure was 72.2 weeks. Study report completed December 17, 2015. No RHC done as part of this study.
- AC-0520377 – open-label 12-week PK/PD (pharmacodynamic) study in 6 Japanese patients less than 15 years of age. Study completed on December 12, 2014. RHC done at baseline and 12 weeks. This study was performed specifically for submission to regulatory authorities in Japan and was not submitted to the NDA for review.

Reviewer comment: Note that with the exception of the Japanese studies, no studies included RHC as a research outcome after the 2002 BREATHE-3 study.

Pediatric Ethics comments included in the 74-day filing review letter to the sponsor and sponsor response:

The following comments were sent to the sponsor in the October 18, 2016 Filing Communication Letter.

“On March 7, 2012, the Agency sent you a general advice letter in response to your Proposed Pediatric Study Request (PPSR), dated September 30, 2011, advising you that use of right heart catheterization (RHC) as a research outcome to assess drug effects on hemodynamic measures in your pediatric trial is more than minimal risk, and that use of RHC as an outcome measure in your studies may not be supportable. Any procedure performed in a pediatric trial solely for the purpose of participating in the trial (i.e., not for a clinical indication) generally may not pose more than a minor increase over minimal risk (21 CFR 50.53). Otherwise, a procedure that presents greater risk may be acceptable only if there is the potential for direct clinical benefit to the individual patients (21 CFR 50.52).

We note that RHC was included as an outcome measure in study AC-052-377 for all patients and in study AC-052-374 (FUTURE 3) in a subset of patients “as per institutional standard.” These studies were conducted after the Agency provided advice on the use of RHC in clinical studies. Please provide further information and clarification on why RHC was performed on these patients, including the clinical guidelines used for deciding when to perform a RHC. Additionally, include information provided to parents as part of the parental permission (informed consent) procedures on the risks of the procedure and the minutes of the institutional review board(s) [IRB(s)] assessment, including the risk determination, for the two studies.

Although AC-052-356 (BREATHE-3) was completed prior to communication with the Agency on RHC as an outcome measure, the Agency requests further information on the IRB(s) assessment, including the risk determination for the study, and the information provided to parents in the parental permission (informed consent) document on the use of RHC as a research outcome measure in the study.”

The sponsor stated that in the FUTURE-3 protocol, the primary efficacy outcome measures, WHO functional class [FC], echocardiography and NT-proBNP (N-terminal prohormone brain natriuretic peptide), were minimal risk procedures. RHC was performed to confirm PAH diagnosis or when clinically required as per pulmonary hypertension guidelines only in bosentan-naïve patients and only at investigational sites where repeated RHC was clinical practice. The pulmonary hypertension guidelines state that RHC may be repeated 3 to 6 months after initiation or changes in therapy in bosentan-naïve patients to confirm efficacy of PAH-specific therapy. The class level of evidence is noted to be Class IIa (weight of evidence/opinion is in favor of usefulness/efficacy) and the level of evidence to be C (Consensus of opinion of the experts and/or small studies, retrospective studies, registries). (Galie et al., 2009) The protocol was developed in 2010 when PVRI obtained via RHC was considered acceptable. The sponsor modified the study in 2012 to limit repeat RHC to patients where previous RHC assessments had not been associated with serious complications. A total of 10/64 patients had repeat testing. The parental permission form included information on the risks of RHC and well as the following:

“A right heart catheterization will only be performed if your child’s doctor thinks this is needed for medical reasons. Right Heart Catheterization is currently the ‘gold standard’ for diagnosing PAH and choosing the appropriate treatment. It is also sometimes repeated to monitor the effect of a new treatment.”

Reviewer comment: *Although the level of evidence based on the guidelines is not strong, the clinical study report (CSR) clearly states that as per the protocol, the procedure must be standard of care at the investigative site.*

For BREATHE-3, the sponsor submitted information on the Institution Review Board (IRB) reviews and information included in the Informed Consent Document (ICD). The study was conducted at 2 sites: Dr. Robyn Barst, Presbyterian Hospital, New York, New York and Dr. Dunbar Ivy, The Children’s Hospital, Aurora, Colorado.

At Dr. Barst’s site, the IRB reviewer requested information on the number of RHCs and whether the RHCs were performed for research purposes only. Dr. Barst replied that the first RHC corresponded with a routine follow-up RHC if they are not new to treatment and that the second RHC was part of the sites “standard of care” as “it helps us determine if there has been any benefit from this new form of treatment.” The IRB provided conditional approval contingent on updating the ICD with the IRB’s requested changes. The ICD included the following language:

“The risks of right heart catheterization include the possibility of bruising (5%) and more serious risks which include infection introduced by the catheter, partial collapse of the lungs or an abnormal heart rhythm as a complication of catheter insertion, perforation of the heart wall, entry of an air bubble into the lung circulation, uncontrolled bleeding, and rarely death. The more serious risks occur less than 1% of the time. You and your child will be explained the risks of the right heart catheterization by the doctor. There may be additional risks, as the right heart catheterizations are being done partly for study purposes.”

The IRB approved the study after the ICD changes were made and reviewed by the board. A pediatric risk assessment using 21 CFR 50 subpart D was not recorded in the IRB approval letter.

At Dr. Ivy's site the IRB required that the ICD clarify whether a second RHC would be performed and the purpose of the RHC ("standard of care" or research) and required a second ICD for the RHC. The IRB stated in the conditional approval letter in regards to required ICD edits: "A second RHC would not be considered standard of care in these subjects. Please clarify." Dr. Ivy included the following language in the ICD:

"Heart Catheterization: You will be explained the risks of the right heart catheterization by the doctor. There are no additional risks for right heart catheterization while participating in this study since it is done as part of the standard of care that patients receive. You will sign a separate consent for the heart catheterization."

The study was approved by the IRB after this change was made. The pediatric risk determination was recorded in the approval documents as 45 CFR 46.405.

Reviewer comment: *The IRB provided a risk determination for Dr. Ivy's site based on Department of Health and Human Services (HHS) regulations. Studies using an investigational agent and performed under IND should be reviewed under 21 CFR 50 Subpart D. The corresponding FDA regulation is 21 CFR 50.52, clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects. For Dr. Barst's site, the IRB did not record a pediatric risk determination in the approval letter. This information may have been recorded in the IRB meeting minutes, but the sponsor states that it is not their practice to request IRB meeting minutes.*

At both sites, the IRB requested clarity on the purpose of the second RHC; however neither IRB appeared to have any objection to the procedure being performed as long as the risks were described adequately in the ICD. Of note, these reviews occurred before the FDA notified the sponsor of concerns related to the risks of RHC in pediatric patients. Without meeting minutes, we cannot determine if a separate analysis of risk was performed in regards to study procedures (i.e., component analysis) at the IRB meeting.

ETHICS CONSULTATION QUESTION(S):

From the Request for Ethics Consultation, July 22, 2015:

"Actelion study AC-052-356, in which Pulmonary Vascular Resistance (PVR) measured by Right Heart Catheterization (RHC) was conducted prior to 2002, will be the clinical data source for a pre-sNDA to add a pediatric indication to NDA 21290, Tracleer. (b) (4)

Please address the ethics of reliance upon study AC-052-356."

ANALYSIS/RESPONSE:

The Additional Safeguards for Children (21 CFR 50 subpart D) must be considered when pediatric patients will be enrolled in a clinical trial. Unless the risks of an investigational agent are no more than a minor increase over minimal risk (21 CFR 50.53), the administration of an investigational agent in children must offer a prospect of direct therapeutic benefit to individually enrolled patients, the risk must be justified by the anticipated benefit, and the anticipated risk-benefit profile must be at least as favorable as that presented by accepted alternative treatments (21 CFR 50.52). Additionally, adequate provisions must be made to obtain the permission on the parents and the assent of the child as per 21 CFR 50.55. There was sufficient data in adult clinical studies to support that bosentan offers a sufficient prospect of direct therapeutic benefit to justify the risks for use in treatment of PAH in pediatric patients, and thus use of the investigational agent in these studies was acceptable and could proceed under 21 CFR 50.52.

In addition to evaluating the risk of the therapeutic agent in a study, the individual risks of interventions or procedures in a research protocol that are not standard of care (and thus do not offer a prospect of direct benefit) must also be evaluated – a approach referred to as "component analysis." If there no direct benefit to pediatric patients (21 CFR 50.52), the risk must either minimal (21 CFR 50.51) or a minor increase over minimal risk (21 CFR 50.53). Additionally (a) the child must have a disorder or condition, and (b) the research

intervention is likely to yield knowledge that is of “vital importance” for understanding or ameliorating the child’s disorder or condition. There is no question that these children have a disorder or condition (PAH) and that PVRI is a valid marker to assess response to treatment, as it is used widely in clinical care for this purpose. The initial RHC, done for diagnostic purposes, is considered to be standard of care, and therefore patients directly benefit, however a second RHC may not be necessary, and if required of all patients in the trial, would need to be considered a minor increase over minimal risk in order to be performed. Although currently we do not consider RHC to be no more than a minor increase over minimal risk, the appropriate standard to apply is our understanding of those risks at the time the studies were performed.

In 2001, both IRBs reviewing BREATHE-3 noted that a second RHC in the studies might be considered as a research only endpoint. We do not have access to the IRB meeting minutes, and therefore we do not know if a “component analysis” was performed. At the time of these reviews, there was limited data on adverse events from the use of RHC in pediatric clinical trials. One site, when asked if the RHC was performed solely for research purposes, responded that they considered the procedure to be standard of care to assess the response to treatment. Both IRBs required that the risks of the procedures be adequately described in the ICD or in a separate document, presumably in an effort to minimize risk. FDA may have considered a RHC to constitute a minor increase over minimal risk at the time of these reviews since there was little information on the risk of RHC in pediatric patients at that time. In 1998, Vitiello published a prospective review of pediatric patients who had undergone cardiac catheterization, noting that previous studies evaluating complication rates with cardiac catheterization had been retrospective. In that study, the majority of adverse event occurred in patients undergoing catheterization for interventional purposes. Complications in patients who had the procedure for diagnostic purposes were reported to be 0.8%. Of the 4952 patients enrolled, seven deaths were reported, all in patients under 5 years of age, four of these catheterizations were done for interventional (and not diagnostic) purposes. For the three patients that died during a diagnostic procedure, all were newborns. Patients enrolled in BREATHE-3 were 3 years of age and older. Although the Division noted this article in their response to the sponsor regarding the use of RHC in 2011 as potential support for not doing RHC, at the time the Division provided that feedback, further data characterizing the risk were available. Studies published prior to the Vitiello article supported a trend towards reduced risks with the procedure as techniques improved. (Cassidy, Schmidt, Van Hare, Stanger, & Teitel, 1992) (b) (4)

(b) (4) We would argue that use of these data is ethical given that at the time the data were collected, the available evidence of risk permitted IRBs to consider RHC to present no more than a minor increase over minimal risk. Of note, the RHCs from the FUTURE-3 study, completed (b) (4) were considered to be done as part of standard of care, and consequently directly benefited the patient (21 CFR 50.52).

RECOMMENDATIONS:

The individual risks of interventions or procedures in a research protocol must be evaluated as part of the risk assessment of a protocol at the time of initial review. If there is no direct benefit to pediatric patients (21 CFR 50.52), the risk of these procedures must either minimal (21 CFR 50.51) or a minor increase over minimal risk (21 CFR 50.53). In the BREATHE-3 trial, the initial RHC was done for diagnostic purposes, is considered to be standard of care, and therefore the procedure directly benefits the patient. However a second RHC done solely for research purposes does not directly benefit the patient and thus must constitute a minor increase over minimal risk in order to be performed as part of a research protocol.

Data collected in the BREATHE-3 trial were collected prior to substantive published literature and the generation of pediatric clinical trial data that described the serious adverse events that may occur with RHC. Consequently, the FDA considered the procedure allowable as a research outcome at the time these studies were conducted. Additionally, until data surfaced (b) (4) calling into question the risk of the procedure, DCRP had allowed repeat RHC as a research outcome to be included in study protocols. We would argue that use of these data is ethical given that at the time the data was collected, the available evidence of risk permitted IRBs to consider RHC to present no more than a minor increase over minimal risk.

REFERENCES:

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Appendix 1

Lethal or serious adverse events associated with right heart catheterization
(from NDA 203109 summary review)

Deaths	
(b) (4)	14 month old male in Poland had a cardiac arrest associated with general anesthesia for right heart catheterization. The subject died. An autopsy performed showed the patient was status-post repair of transposition of great arteries. And status post excision of intra-atrial septum. The autopsy diagnosis was consistent with pulmonary hypertension as the cause of death.
(b) (4)	5 year old female who was pretreated for catheterization with ketamine and midazolam. Post-procedure the child developed bradycardia and hypotension which temporarily responded to resuscitation. The subject however arrested in the ICU and died. It is unclear if an autopsy was performed.
Serious Adverse events pre-randomization	
(b) (4)	4 year old Polish female developed complete A-V block during pre-randomization catheterization. She was treated with isoproterenol and the blockade resolved.
(b) (4)	4 year old Polish male, developed right ventricular insufficiency and edema during catheterization. The child was treated with oxygen, diuretics and dopamine. Chest X-ray showed cardiomegaly and decreased vascular markings. The subject was discharged after 9 days.
Serious Adverse events end of 16-week study	
(b) (4)	This was a 3 year old Asian male who in preparation for end of double-blind study right heart catheterization received midazolam and ketamine. The subject desaturated, developed bronchospasm, respiratory distress and bradycardia. He was treated with oxygen, steroids, and B ₂ agonists, as well as received bag and mask ventilation. The bronchospasm, respiratory distress and bradycardia resolved after 3 days.

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/s/

DONNA L SNYDER
01/12/2017

ROBERT M NELSON
01/12/2017

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 11/23/2016

TO: Division of Cardiovascular and Renal Products
Office of Drug Evaluation I

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 209279

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data for Study AC-052-116 without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS has no inspectional history of the site listed below. However, we are aware that (b) (4) closed its operations in 2012 and all the records/raw data pertaining to Study AC-052-116 were transferred to the applicant, Actelion Pharmaceuticals, Ltd. located in Allschwil, Switzerland. Because the Division of Cardiovascular and Renal Products has not identified specific concerns that would need to be evaluated during an inspection, and such an inspection would be limited to a record audit at the applicant, an inspection is not warranted at the current time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	(b) (4)

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/s/

SHILA S NKAH
11/23/2016