CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209279Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
ODE 1
Division of Cardiovascular and Renal Products

NDA/BLA #s:	209279
Products:	Tracleer (bosentan) Dispersible Tablets
APPLICANT:	Actelion Pharmaceuticals
FROM:	Mary Ross Southworth, PharmD
DATE:	September 5, 2017

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Tracleer (bosentan) Dispersible Tablets to ensure that the benefits of the drug outweigh the risks of hepatotoxicity and teratogenicity. Of note, the elements of this REMS are the same as those for Tracleer Tablets (NDA 21290), which contain the same active ingredient as Tracleer Dispersible Tablets (NDA 209279). The REMS for Tracleer (bosentan) was originally approved on August 7, 2009. In reaching this determination, we considered the following:

A. Tracleer Dispersible Tablets will be indicated for the treatment of WHO Group 1 pulmonary arterial hypertension (PAH). The exact number of people affected with pulmonary hypertension in the United States is unknown; based on registry data, prevalence rates are approximately 10-26 per million[1]

B. Pulmonary hypertension is associated with significant morbidity and mortality. Symptoms

[1] McGoon MD, Benza RL, Excribano-Subias, et al. Pulmonary Arterial Hypertension: Epidemiology and Registries, J Am Coll Cardiol 2013; 62: D51.

include decreased exercise tolerance, shortness of breath, and fatigue; symptoms often may lead to hospitalization. Disease progression eventually leads to right ventricular heart failure. The mortality rate at 1 year is approximately 15%.

C. Tracleer (bosentan) is approved to improve exercise ability and decrease clinical worsening in patients with PAH. Clinical worsening includes hospitalization for PAH and need for parenteral epoprostenol therapy.

D. Tracleer will be used chronically.

E. Tracleer is associated with teratogenicity (based on animal studies) and hepatotoxicity (seen in the clinical studies and in post-marketing period).

F. Tracleer (bosentan) is not a new molecular entity.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. FDA has determined that Tracleer (bosentan) Dispersible Tablets pose a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Tracleer (bosentan) Dispersible Tablets. FDA has determined that Tracleer (bosentan) Dispersible Tablets are products for which patient labeling could help prevent serious adverse effects and that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use Tracleer (bosentan) Dispersible Tablets. Under section 505-1 of the FDCA, FDA has also determined that a Medication Guide is necessary to ensure the benefits of the drug outweigh the risk(s) of hepatotoxicity and teratogenicity.

The elements of the REMS will be a Medication Guide, an implementation system, a timetable for submission of assessments of the REMS, and elements to assure safe use, including:

- Healthcare providers have particular experience or training, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions

Tracleer Dispersible Tablets will be subject to the same REMS as Tracleer (bosentan) Tablets (NDA 21290), known as the Tracleer REMS. Consequently, Tracleer Dispersible Tablets will be subject to the same REMS assessment plan in the Tracleer REMS, and align with the subsequent assessments of the Tracleer REMS.

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/s/

MARY R SOUTHWORTH
09/05/2017

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW

Date:	August 31, 2017
Reviewers:	Theresa Ng, Pharm.D. BCPS, CDE Risk Management Analyst Division of Risk Management (DRISK) Joan E. Blair, RN, M.P.H., Health Communication Analyst, DRISK
Team Leader:	Leah Hart, Pharm.D., DRISK
Deputy Division Director:	Jamie Wilkins Parker, Pharm.D. DRISK
Drug Name(s):	Tracleer (bosentan) Dispersible Tablet
Therapeutic Class:	Endothelin Receptor Antagonist
Dosage and Route:	(b) (4) orally twice daily
OND Review Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type/Number:	NDA 209279
Supplement #:	
PDUFA/Action Date:	September 5, 2017
Applicant:	Actelion Pharmaceuticals, Inc.
OSE RCM #:	2016-1912

Table of Contents

1. Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed risk evaluation and mitigation strategy (REMS) for Tracleer (bosentan) NDA 209279, a new dispersible tablet formulation for the treatment of pulmonary arterial hypertension (PAH) in pediatric patients. Bosentan, under the same proprietary name, Tracleer, is currently approved with a REMS consisting of a Medication Guide (MG), Elements to Assure Safe Use (ETASU) and an implementation system under NDA 21290. The existing REMS is designed to mitigate the risks of hepatotoxicity and minimize the risk of fetal exposures in female patients who are exposed to Tracleer.

This review follows the DRISK review dated 6/2/17 which included redlined documents aligning the new indication and NDA number with the Prescribing Information (PI). Furthermore, the Agency informed the Sponsor to delete (b) (4) . The amendment received June 21, 2017 incorporates the Agency's changes.

Actelion submitted an additional amendment on 8/2/17 to include NDA 21290 in the REMS Document as both Tracleer products (NDA 209279 and NDA 21290) will share a REMS and PI. Additionally, the Sponsor made additional editorial changes to the Prescriber and Pharmacy Guide and REMS website.

1.1 Product Background

Bosentan is an oral endothelin receptor antagonist approved in November 2001 for PAH. Currently, Tracleer is indicated for the treatment of PAH (WHO Group 1) to improve exercise ability and to delay clinical worsening. Bosentan is currently available in 62.5 and 125 mg film-coated tablets for oral administration. The recommended dose for PAH in adults is 62.5 mg twice daily for 4 weeks with an increase to the maintenance dose of 125 mg twice daily. The proposed pediatric dosage for patients under 12 years of age is as follows:

Weight	Initial and Maintenance dosing
4 - 8 kg	16 mg twice daily
Greater than 8 - 16 kg	32 mg twice daily
Greater than 16 - 24 kg	48 mg twice daily
Greater than 24 - 40 kg	64 mg twice daily
Greater than 40 kg	62.5 mg twice daily

1.2 Regulatory History

The following is a summary of the regulatory history relevant to this review:

August 5, 2016: Actelion submitted NDA 209279,a dispersible tablet formulation of bosentan for PAH in the pediatric population. This REMS proposal, if approved will require a modification to the existing Tracleer (NDA 21290) REMS with an update of the pediatric indication and NDA number as they will share REMS materials and PI.

August 22, 2016: Actelion submitted amended REMS materials to NDA 209279.

December 16, 2016: The Agency approved S-30 for Tracleer, NDA 21290 which included a REMS Modification to add new forms for Veterans Affairs use along with changes to update patient consent language and remove non-REMS information from REMS materials.

January 30, 2017: Actelion submitted amended REMS materials to NDA 209279 to include updates to the REMS materials in response to the December 16, 2016 Tracleer (NDA 21290) modification.

May 31, 2017: Communication from Agency requesting Actelion to : 1) remove proposed language (b) (4) , and 2) include the proposed pediatric indication in the website and REMS materials to align with the PI. In addition, redlined REMS materials were sent to Actelion.

June 2, 2017: The May 31st review and subsequent communication to the Sponsor contained documents with minor formatting errors. Corrected redlined documents were sent to the Sponsor including a Pharmacy Inpatient Enrollment Form which was not previously included in the appended redlined REMS materials. The Sponsor was instructed to revise the REMS materials based on this communication. A corrected REMS review was also finalized.

June 21, 2017: Actelion submitted amended REMS materials in response to the June 2, 2017 communication.

July 26, 2017: The Agency received an email communication from Actelion stating that they will be submitting an amendment including a minor editorial change to the dispersible tablet (NDA 209279) REMS, and that they will be submitting a minor modification to the Tracleer 21290 REMS to align the REMS of the two Tracleer products. The Agency responded to the communication and requested that Actelion submit the amendments/modifications with the NDA number (Tracleer NDA 21290 and Tracleer NDA 209279 dispersible tablets) for both products on the REMS Documents as they will share REMS and PI.

August 2, 2017: Actelion submitted a minor modification in response to the Agency's communication dated 7/26/17.

August 11, 2017: Agency sent a correspondence to Actelion noting that the indication statement in the materials should align with the PI and therefore requested updates to the language included in the indication statement in the REMS materials.

August 25, 2017: Actelion submitted amendment to align the indication statement as requested in the Agency's 8/11/17 IR.

2. Materials Reviewed

The following is a list of materials used to inform this review:

- Actelion Pharmaceuticals. Bosentan NDA 209279 submission, <eCTD Sequence 0000>, Original 1, dated August 5, 2016
- Actelion Pharmaceuticals. Bosentan NDA 209279 submission, <eCTD Sequence 0001>, Original 1, dated August 22, 2016
- REMS for TRACLEER (bosentan), NDA 21290, modified December 16, 2016
- Actelion Pharmaceuticals. Bosentan NDA 209279 submission, <eCTD Sequence 0018>, Original 1, dated January 30, 2017
- Sheppard, J. REMS Review for Tracleer (bosentan) Dispersible Tablet (NDA 209279), dated June 2, 2017

- Actelion Pharmaceuticals. Bosentan NDA 209279 submission, <eCTD Sequence 0036>, Original 1, dated June 21, 2017
- Actelion Pharmaceuticals. Bosentan NDA 209279 submission, <eCTD Sequence 0042>, Original 1, dated August 2, 2017
- Actelion Pharmaceuticals. Proposed USPI NDA 209279, <eCTD sequence. 0045>, Original 1, dated August 18, 2017
- Actelion Pharmaceuticals. Bosentan NDA 209279 <eCTD sequence 0047>, Original 1, dated August 25, 2017

3. Results of Review of Proposed REMS

Actelion incorporated all the Agency's changes as requested in the June 2, 2017 REMS review. The REMS Document and appended materials are updated with information such as the NDA number for both Tracleer products and the pediatric and adult indications to align with the proposed PI. In addition, the REMS Supporting Document is updated to align with the REMS Document, and all non-risk related statements have been removed from the REMS materials.

In addition Actelion made the following global changes:

- minor typographical and editorial changes
- updated version control
- added the word "REMS" to the REMS materials to clarify the intended use and maintain consistency with naming of REMS forms.

REMS Appended Materials

Additional proposed changes to the REMS are listed below:

Prescriber and Pharmacy Guide for the Tracleer REMS Program

- Added detailed monitoring instructions in the Tracleer aminotransferase (ALT/AST) management section in alignment with the PI. This includes specific categories of ALT/AST levels and treatment and monitoring recommendations.

ALT/AST level	Treatment and monitoring recommendations
≤3 × ULN*	**Continue** to monitor; no change in monitoring schedule or dosage
>3 to ≤5 × ULN	**Confirm** by another aminotransferase test; if confirmed, - in adults and pediatric patients >12 years and >40 kg, reduce the daily dose to 62.5 mg twice daily or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pretreatment values, treatment may continue or be reintroduced at 62.5 mg twice daily, with reassessment of aminotransferase levels within 3 days. - in all other pediatric patients, interrupt treatment with no prior dose reduction. If the aminotransferase levels return to pretreatment values, reintroduce at the dose used prior to treatment interruption, with reassessment of aminotransferase levels within 3 days.
>5 to ≤8 × ULN	**Confirm** by another aminotransferase test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pretreatment values, - in adults and pediatric patients >12 years and >40 kg, consider reintroduction of treatment at 62.5 mg twice daily, with reassessment of aminotransferase levels within 3 days. - in all other pediatric patients, consider reintroduction at the dose used prior to treatment interruption, with reassessment of aminotransferase levels within 3 days.
>8 × ULN	**Stop** treatment permanently. There is no experience with reintroduction of Tracleer in these circumstances.

Reviewer Comment: We agree to the addition of specific information for the AST/ALT monitoring as it aligns with the Tracleer PI.

3.1 REMS Supporting Document and Assessment Plan

Actelion incorporated the recommendations from the Agency and the assessment plan aligns with the approved assessment plan for The Tracleer (NDA 21290) REMS.

4. Discussion

Actelion submitted Tracleer (bosentan) NDA 209279, a new dispersible tablet formulation of Tracleer for treatment PAH in the pediatric population. As there is an existing approved Tracleer REMS, and the risks for the dispersible tablet formulation do not differ from that of the currently approved product, a REMS is necessary to ensure that the benefit outweighs the risks. The proposed Tracleer NDA 209279 REMS

will be harmonized upon approval with the REMS for Tracleer NDA 21290 including the addition of the pediatric indication and new NDA number. All non-risk related statements such as product specific dispersible tablet formulation, the Healthcare provider letter, and "Changes to Tracleer REMS Program" sections are removed from the REMS materials. Additionally, the REMS Document, all REMS materials and the REMS website are updated to align with the PI. Finally, the REMS Supporting Document has been appropriately updated.

The Office of Prescription Drug Promotion (OPDP) provided the following comments on the materials on June 30, 2017:

OPDP considers the following statements promotional in tone and recommends revising or deleting them from the REMS piece:

- Prescriber and Pharmacy Guide for the Tracleer REMS Program
- Tracleer REMS Inpatient Pharmacy Enrollment Form
- Tracleer REMS Program Website
    - These REMS pieces include several instructions for healthcare providers to educate and counsel females of reproductive potential on the "risk of **teratogenicity**" (emphasis added).
        - **Risk**
            - These presentations may minimize the REMS related risk of embryo-fetal toxicity by using a different term (i.e., teratogenicity) to communicate the Boxed Warning of embryo-fetal toxicity, thereby dissociating the risk of embryo-fetal toxicity from Tracleer specifically (emphasis added). We note that throughout the Tracleer PI, the term "embryo-fetal toxicity" is used to reference this important REMS related risk (please see *Boxed Warning, Warnings and Precautions (5.2), Adverse Reactions, Use in Specific Populations (8.1),* and *Patient Counseling Information)*. We recommend revising these REMS pieces to include the term "embryo-fetal toxicity" to be consistent with the Tracleer PI.

The Division of Risk Management (DRISK) considered OPDP's comments and noted OPDP's concerns. DRISK is aware that the three REMS materials noted above use the term "teratogenicity" vs. "embryo-fetal toxicity," and that they do not align with the Tracleer PI. However, DRISK recommends that the REMS materials retain the "teratogenicity" term for now to align with the REMS Document. Changes to align terminology will occur with the forthcoming approval of the Bosentan Single Shared System REMS. The retention of these terms do not pose a safety issue. Therefore, at this time DRISK did not accept the OPDP comments, and upon discussion with OPDP, they expressed understanding of DRISK's response.

Therefore, DRISK agrees with all proposed changes to the REMS and materials for NDA 209279 as submitted on August 25, 2017 .

5. Conclusion and Recommendation

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

APPENDIX

Tracleer REMS Document

Tracleer REMS Prescriber Enrollment and Agreement Form

Tracleer REMS Patient Enrollment and Consent Form

Tracleer REMS Patient Enrollment and Consent Form- VA use

Prescriber and Pharmacy Guide for the Tracleer REMS Program

Tracleer REMS Guide for Patients

Tracleer REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form

Tracleer REMS Inpatient Pharmacy Enrollment Form

Tracleer REMS Website

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/s/

THERESA N NG
08/31/2017

JAMIE C WILKINS PARKER
09/01/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	June 2, 2017
Reviewer:	Jacqueline Sheppard, Pharm.D. Division of Risk Management Joan Blair, RN, M.P.H Division of Risk Management
Team Leader (Acting):	Leah Hart, Pharm.D. Division of Risk Management
Deputy Director:	Jamie Wilkins Parker, Pharm.D., Division of Risk Management
Subject:	Evaluation of proposed REMS modification to Tracleer for the proposed indication of pulmonary arterial hypertension in pediatric patients and a new dispersible tablet formulation
Drug Name:	Tracleer (bosentan) Dispersible Tablet
Therapeutic Class:	Endothelin Receptor Antagonist antagonist
Indications:	Pulmonary Arterial Hypertension in the Pediatric Population
Dosage and Route:	(b) (4) orally twice daily
Application Type/Number:	NDA 209279
Applicant:	Actelion Pharmaceuticals
OSE RCM #:	2017-132

1. INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates the proposed risk evaluation and mitigation strategy (REMS) for NDA 209279, Tracleer (bosentan), for the indication of pulmonary arterial hypertension (PAH) in pediatric patients and a new dispersible tablet dosage formulation. Bosentan has been previously approved with a REMS consisting of a Medication Guide (MG), Elements to Assure Safe Use (ETASU) and an implementation system under NDA 21290 for the treatment of PAH. The currently approved REMS is designed to mitigate the risks of hepatotoxicity and minimize the risk of fetal exposures in patients who are exposed to Tracleer.

Actelion Pharmaceuticals submitted an application with a proposed REMS for NDA 209279 on August 5, 2016. The Sponsor amended the proposed REMS on August 22, 2016 and January 30, 2017 to align the proposed REMS with the Tracleer REMS modifications approved on December 16, 2016. This REMS proposal if approved will require a modification to the existing Tracleer (NDA 21290) REMS as the two NDAs will share Prescribing Information and REMS materials.

1.1. DISEASE BACKGROUND

Pulmonary arterial hypertension (PAH) is a progressive disorder characterized by increased pulmonary vascular resistance and pulmonary pressures leading to reduced cardiac output, right heart failure and death. PAH can be idiopathic, familial, or associated with other medical condition such as HIV, congenital heart disease or persistent pulmonary hypertension of the newborn. Diagnosis of PAH is confirmed when the mean PA (pulmonary arterial) pressure exceeds 25 mmHg and the PA occlusion pressure or pulmonary capillary wedge pressure is less than 15 mmHg. PAH is a rare disease with a prevalence in the general population estimated at 10 – 52 cases per million.[1] There are currently no approved therapies for the management of PAH in pediatric patients in the US. The 32 mg dispersible tablet represents the first therapeutic option to be approved for the treatment of pediatric PAH. See Table 1 for the current treatment scheme for PAH.

Table 1. Current therapies in the treatment of PAH

Drug Name	Dosage Form	Warning and Precaution	Box Warning	REMS
Endothelin Receptor Antagonists				
ambrisentan (Letairis)	5 mg, 10 mg oral tablets	Embryo-fetal toxicity, fluid retention, pulmonary edema, decreased sperm counts, hematological changes	Embryo-fetal toxicity	Embryo-fetal toxicity (ETASU)
bosentan (Tracleer)	62.5 mg, 125 mg oral tablets	Hepatoxicity, Embryo-fetal toxicity, fluid retention, pulmonary veno-occlusive disease, decreased sperm counts, hematological changes	Embryo-fetal toxicity; Hepatotoxicity	Embryo-fetal toxicity and Hepatotoxicity (ETASU)
macitentan (Opsumit)	10 mg oral tablets	Hepatoxicity, Embryo-fetal toxicity, fluid retention, pulmonary edema, decreased sperm counts, hematological changes	Embryo-fetal toxicity	Embryo-fetal toxicity (ETASU)

riociguat (Adempas)	0.5 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg oral tablets	Embryo-fetal toxicity, hypotension, bleeding, pulmonary veno-occlusive disease	Embryo-fetal toxicity	Embryo-fetal toxicity (ETASU)
Prostacylin vasodilator				
epoprostenol (Flolan, Veletri)	Flolan: 0.5 mg/vial or 1.5 mg/vial powder for injection Veletri: 1.5 mg/vial for injection	Pulmonary Edema, rebound pulmonary hypertension, vasodilation reactions, increased risk for bleeding	No	No
treprostinil (Orenitram, Remodulin, Tyvaso)	Orenitram: 0.125 mg, 0.25 mg, 1 mg, 2.5 mg, 5 mg extended-release oral tablets Remodulin: 1 mg/ml, 2.5 mg/ml, 5 mg/ml, 10 mg/ml vials for injection Tyvaso: 0.6 mg/ml ampule for inhalation	Orenitram: Increased risk for bleeding Remodulin: risk of blood stream infections and sepsis Tyvaso: systemic hypotension, increased risk of bleeding	No	No
Prostacyclin analog				
iloprost (Ventavis)	10 mcg/ml, 20 mcg/ml ampules for inhalation	Hypotension, pulmonary venous hypertension, bronchospasm	No	No
Prostacyclin receptor agonist				
selexipag (Uptravi)	200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg, 1600 mcg oral tablets	Pulmonary edema	No	No
Phosphodiesterase-5 (PDE-5) Inhibitor				
sildenafil (Revatio)	20 mg oral tablet; 10 mg/12.5 ml injection; 10 mg/ml oral solution	Increased mortality with increasing doses in pediatric patients; vasodilation effects; pulmonary edema; hearing or visual impairment; serious vaso-occlusive crises	No	No
tadalafil (Adcirca)	20 mg oral tablets	Cardiovascular effects; vision loss; hearing impairment, prolonged erection	No	No

1.2. PRODUCT BACKGROUND

Bosentan is an oral endothelin receptor antagonist approved in November 2001 for the treatment of PAH. Currently, Tracleer is indicated for the treatment of PAH (WHO Group 1) to improve exercise ability and to delay clinical worsening. Bosentan is currently available in 62.5 and 125 mg film-coated tablets for oral administration. The recommended dose for PAH in adults is 62.5 mg twice daily for 4 weeks with an increase to the maintenance dose of 125 mg twice daily. The proposed pediatric dosage for patients under 12 years of age is as follows:

Weight	Initial and Maintenance dosing
4 - 8 kg	16 mg twice daily
Greater than 8 - 16 kg	32 mg twice daily
Greater than 16 - 24 kg	48 mg twice daily
Greater than 24 - 40 kg	64 mg twice daily
Greater than 40 kg	62.5 mg twice daily

1.3. REGULATORY HISTORY

The following is a summary of the regulatory history relevant to this review:

November 20, 2001: The Agency approved bosentan (NDA 21290) for the treatment of pulmonary arterial hypertension. The application was approved with a risk mitigation program that included a Medication Guide and a restricted distribution system.

March 27, 2008: The risk mitigation program for bosentan (NDA 21290) was deemed to have in effect an approved REMS.

August 7, 2009: The Agency approved S-16 for NDA 21290 which provided for a REMS consisting of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments.

August 5, 2015: Actelion submitted NDA 209279 which a dispersible tablet for the indication of the treatment of PAH in the pediatric population. This REMS proposal if approved will require a modification to the existing Tracleer (NDA 21290) REMS.

August 22, 2016: Actelion submitted amended REMS materials to include tracked changes of materials that have proposed differences from the RLD, NDA 21290.

December 16, 2016: The Agency approved S-30 for NDA 21290 which included a REMS Modification to add new forms for Veterans Affairs use along with changes to update patient consent language and remove non-REMS information from REMS materials.

January 30, 2017: Actelion submitted amended REMS materials to include updates to the REMS materials in response to the December 16, 2016 Tracleer (NDA 21290) modification.

2. MATERIALS REVIEWED

The following is a list of materials used to inform this review:

- Actelion Pharmaceuticals. Bosentan NDA 209279 submission, <eCTD Sequence 0000>, Original 1, dated August 5, 2016.
- Actelion Pharmaceuticals. Bosentan NDA 209279 submission, <eCTD Sequence 0001>, Original 1, dated August 22, 2016.
- Actelion Pharmaceuticals. Bosentan NDA 209279 submission, <eCTD Sequence 0018>, Original 1, dated January 30, 2017.
- Draft Prescribing Information, NDA 209279, April 3, 2017
- REMS for TRACLEER (bosentan), BLA 21290, modified December 16, 2016
- Gordon, M. DCRP. Clinical Review for Tracleer (NDA 209279), dated March 22, 2017.
- Garnett C, Florian J. Clinical and Clinical Pharmacology Efficacy Review for Tracleer (NDA 209279), dated March 31, 2017.

3. RESULTS OF REVIEW

3.1. OVERVIEW OF CLINICAL PROGRAM

The efficacy of bosentan for the treatment of PAH in children was evaluated in a clinical program that included three open-label, uncontrolled studies. The study participants ranged from 3 months to 15 years of age with a diagnosis of PAH. One of the three studies (BREATHE 3) used the commercially available film-coated tablet and two other studies (FUTURE 1 and 3) used the proposed 32 mg dispersible tablet.

The Agency's analysis of the data is described in Section 3.2 below.

3.2. SUMMARY OF EFFICACY

The BREATHE 3 study was a 12- week open-label, parallel, single and multiple dose, uncontrolled phase 3 study which enrolled 19 patients aged between 3 and 15 years on conventional vasodilator/anticoagulant therapy or epoprostenol therapy. The primary objective was to investigate the PK of bosentan given as single and multiple oral doses in pediatric patient with PAH. The primary efficacy endpoint was a change in baseline to week 12 in pulmonary vascular resistance (PVR) and pulmonary vascular resistance index (PVRI). At the end of the study, 5 patients (26%) improved by one World Health Organization Functional Class (WHO FC).

The FUTURE 1 study was a 12- week open-label, single-arm, uncontrolled phase 3 study which examined 36 patients aged 2 to 12 years of age. Patients were either treatment naïve, treated with bosentan, intravenous epoprostenol, or intravenous or inhaled iloprost. The primary objective was to demonstrate that exposure to bosentan in pediatric patients with idiopathic pulmonary hypertension (IPAH) or familial PAH using a pediatric formulation was similar to that in adults with PAH. The primary efficacy endpoints were 1) change from baseline to end of study in WHO functional class, quality of life questionnaire score, Global clinical impression scale (GCIS) according to the parents, GCIS according to the physician 2) PAH worsening endpoints including time to death or first occurrence of transplantation or hospitalization or time to initiation of new therapy or new or worsening right heart failure. At the end of the study, WHO FC improved in 11/28 patients (39%) while worsening was reported for two patients who

discontinued because of death or disease progression. GCIS as rated by parents improved from baseline in 13/16 patients (81%) with available data and GCIS as rated by physicians improved from baseline in 17/26 patients (65%) with available data.

The FUTURE 3 core study was a prospective, open-label, randomized, comparative, parallel group, uncontrolled phase 3 study which examined 64 patients aged 3 months or greater to 12 years of age. Patients were randomized to receive oral doses of bosentan as an aqueous dispersion at doses of 2 mg/kg BID or TID as well as other prostanoids or phosphodiesterase type-5 inhibitors. The primary objective was to investigate the PK of the dispersible tablet formulation of bosentan at doses of 2 mg/kg BID and 2 mg/kg TID in children with PAH. The primary efficacy endpoints were 1) change in in baseline of pulmonary vascular resistance index (PVRI) and other hemodynamic variables including pulmonary arterial systolic, diastolic and mean pressure, cardiac output, and cardiac index 2) change in baseline in echocardiography/Doppler variables and plasma NT-proBNP and 3) PAH worsening endpoints.

The FUTURE 3 extension study was an open-label, double-arm, uncontrolled extension to the future trial. 58 patients in the FUTURE 3 core study continued to receive either 2 mg/kg BID or TID for 12 months. Including data from the extension study, 50/64 (78%) of patients had no change from baseline at month 18 in WHO FC for all treatment sets. At Month 18, physicians' GCIS remained unchanged for 21/64 (56.87%) of patients, improved for 11/64 (30%) of patients, and worsened for 5/34 (13.5%) of patients. The results for the parents' / legal representatives' GCIS rating were similar to those for the physicians' GCIS rating.

3.3. SUMMARY OF SAFETY

The safety data from the pediatric indication studies are consistent with the other approved indication.

3.3.1. Deaths

There were 15 deaths that occurred during the phase 3 studies. There were 10 deaths related to cardiovascular events (fever, low cardiac output and right cardiovascular output leading to cardiac arrest in a 10 year old female; worsening PAH followed by cardiac arrest in a 5 year old male; worsening PAH leading to cardiac failure in a 7 year old male; PAH progression in a 4 year male;; acute right heart failure and bradycardia in a 3 year old female; acute heart failure resulting from mucopolysaccharidosis in a 6 year old male; thromboembolism of the pulmonary artery in a 3 year old female; PAH progression in a 4 year old male; worsening PAH in a 10 year old female; worsening PAH in an 11 year old male.)

There was one death related to surgical complication (refractory right ventricular failure after Potts anastomosis in a 5 year old male.)

There were 4 deaths related to infection (pneumonia in a 8 year old female; bronchopneumonia in a 14 month old male, respiratory syncytial virus and sepsis in a 3 year old male; acute pneumonia in a 0.6 month old male; pneumonia in a 22 month old female.)

The clinical reviewer concurs that no death in the pediatric PAH program can be conclusively linked to the use of bosentan.[2]

4. Currently Approved REMS

Bosentan's REMS currently includes a MG, ETASU, implementation system, and a timetable for submission of assessments. The goals of the REMS are 1) to inform prescribers, patients, and pharmacists about the risks of Tracleer 2) to minimize the risk of hepatotoxicity in patients who are exposed to Tracleer 3) to minimize the risk of fetal exposures in female patients who are exposed to Tracleer and 4) to educate prescribers, patients, and pharmacies on the safe-use conditions for Tracleer. The professional labeling for Tracleer includes these risks in the Warnings and Precautions section of the label and in the boxed warning. In order to ensure safe use conditions are being met, prescribers and pharmacies are required to certify and patients are required to enroll in the REMS program and subject to hepatotoxicity and pregnancy testing.

5. Proposed REMS

Actelion submitted a proposed REMS with this application, which if approved, would also require a REMS modification to NDA 21290, the RLD. (b) (4) As such, the Agency has rejected these changes as detailed in the attached red-lined documents. Any additional changes are noted below.

5.1. REMS DOCUMENT

The Agency reviewed the REMS document submitted by Actelion Pharmaceuticals on August 5, 2016. The Agency made minor editorial changes to add the NDA number to the document. These changes are detailed in the attached redlined document.

5.2. REMS APPENDED MATERIALS

The Agency reviewed the REMS materials submitted by Actelion Pharmaceuticals on August 5, 2016 and amended on August 22, 2016 and January 30, 2017. Please see attached redlined documents for edits.

5.3. REMS SUPPORTING DOCUMENT AND ASSESSMENT PLAN

Actelion did not provide changes to the Supporting Document; however revisions are needed to align the Supporting Document with the Agency revisions to the REMS Document.

6. DISCUSSION

The safety data from the pediatric studies and those of the dispersible tablet formulation studies were consistent with the other approved indication and dosage form. Bosentan (NDA 21290) was initially approved for the treatment of pulmonary arterial hypertension in November 2001 with a risk mitigation program that included a Medication Guide and a restricted distribution system and was deemed to have in effect an approved REMS in March 2008. The currently approved REMS is designed to mitigate the risks of hepatotoxicity and minimize the risk of fetal exposures in patients who are exposed to Tracleer.

DRISK and DCRP concur that a REMS is necessary to ensure the benefits outweigh the risks for Tracleer for the proposed treatment of PAH in pediatric patients and for the new dispersible

tablets (NDA 209279). The approval of the proposed REMS would also require a REMS modification to the currently approved Tracleer REMS.

We reviewed the proposed REMS submitted by Actelion on August 5, 2016 and amended on August 22, 2016 and January 30, 2017 for NDA 209279. The submissions update the REMS materials (b) (4) As such, the Agency has rejected these changes as detailed in the attached red-lined documents.

However in order to align the REMS materials with the current PI, Actelion should ensure that the indication statement is updated to address the pediatric indication in the website and REMS materials that currently contain the indication statement. Additionally, the Agency added the NDA number to the REMS Document. See attached redlined documents.

Furthermore, Actelion should also update the Supporting Document to align with the changes to the REMS document.

Finally, DRISK agrees with all other previously mentioned revisions, additions, and deletions made to the REMS Document, appended materials, and Supporting Document unless otherwise noted above.

7. CONCLUSION AND RECOMMENDATIONS

Based on the available data, a REMS is needed to ensure the benefits outweigh the risks for the pulmonary arterial hypertension in pediatric patients and the new dosage form of dispersible tablets. However, DRISK does not agree with all of the Actelion's proposals for the REMS submitted under NDA 209279. Comments for the Sponsor are provided in Section 8.

8. COMMENTS FOR THE SPONSOR

The comments in the attached red-lined documents are based on the Agency's review of the proposed REMS for Tracleer submitted under NDA 209279. In order to facilitate further review, we ask that you respond to these comments within 14 business days.

A. General Comments

1. (b) (4) See the attached red-lined documents.
2. Update the indication statement to include the proposed pediatric indication in the website and REMS materials that currently contain an indication statement. This is required in order to align the REMS materials with the current Prescribing Information.
3. Your next submission should include clean MS word, tracked MS word, and formatted pdf version of all materials (including those not specifically commented upon in this communication). All content in the materials must align with the REMS document and the Prescribing Information and must include content that is consistent across all of the REMS materials and website.

B. REMS Document

1. The Agency has made minor editorial changes. See attached redlined document.

Attachments

REMS Document

Prescriber and Pharmacy Guide for the Tracleer REMS Program

Tracleer REMS Guide for Patients

Dear Healthcare Provider Letter

Tracleer REMS website

[1] Humbert M, Sitbon O, Simonneau G. Treatment of Pulmonary Arterial Hypertension. N Engl J Med 2004; 351:1425-1436

[2] Gordon, M. DCRP. Clinical Review for Tracleer (NDA 209279), dated March 22, 2017.

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

/s/

JACQUELINE E SHEPPARD
06/02/2017

JAMIE C WILKINS PARKER
06/02/2017