# Cross-Discipline Team Leader Review

<table>
<thead>
<tr>
<th>Date</th>
<th>September 4, 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>From</td>
<td>Aliza Thompson, Clinical Team Leader, Division of Cardiovascular and Renal Products (DCRP)</td>
</tr>
<tr>
<td>Risk Benefit Assessment co-authored by</td>
<td>Norman Stockbridge, Division Director, DCRP</td>
</tr>
<tr>
<td>Subject</td>
<td>Cross-Discipline Team Leader Review</td>
</tr>
<tr>
<td>NDA#</td>
<td>209279</td>
</tr>
<tr>
<td>Applicant</td>
<td>Actelion Pharmaceuticals, Ltd.</td>
</tr>
<tr>
<td>Date of Submission</td>
<td>August 5, 2016</td>
</tr>
<tr>
<td>PDUFA Goal Date</td>
<td>September 5, 2017 (extended from June 5, 2017 because of a major amendment)</td>
</tr>
<tr>
<td>Proprietary Name / Established (USAN) names</td>
<td>Tracleer (bosentan)</td>
</tr>
<tr>
<td>Dosage forms / Strength</td>
<td>Dispersible Tablets 32 mg</td>
</tr>
<tr>
<td>Proposed Indication(s)</td>
<td>Tracleer® is 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 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%).</td>
</tr>
</tbody>
</table>
| Recommended: | Approval for the following indications: Tracleer® is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1):  
- in adults to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness in adults included predominantly patients with WHO 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%)  
- in pediatric patients aged 3 years and older with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability |
This secondary review is based on the following reviews:

<table>
<thead>
<tr>
<th>Material Reviewed/Consulted</th>
<th>Team Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality Assessment (8/7/17)</td>
<td>Stephanie Emory, Peter Guerreier, Zhong Li, Joan Zhao, Dahlia Woody, Mohan Sapru (Application Technical Lead)</td>
</tr>
<tr>
<td>Pharmacology Toxicology Review (3/20/17)</td>
<td>John Koerner, Albert DeFelice</td>
</tr>
<tr>
<td>Clinical Pharmacology Review (4/11/17)</td>
<td>Venkateswaran Chithambaram Pillai, Sudharshan Harharan</td>
</tr>
<tr>
<td>Clinical Review (3/22/17)</td>
<td>Maryann Gordan</td>
</tr>
<tr>
<td>Division of Pediatric and Maternal Health Memorandum, Pregnancy and Lactation labeling (3/30/17)</td>
<td>Jane Liedtka, Lynne P. Yao</td>
</tr>
<tr>
<td>Office of Pediatric Therapeutics (1/12/17)</td>
<td>Donna Snyder</td>
</tr>
<tr>
<td>Division of Medication Error Prevention and Analysis Reviews (3/8/, 8/16 (x2), and 8/31/17)</td>
<td>Sarah Thomas, Chi-Ming (Alice) Tu, Daniele Harris</td>
</tr>
<tr>
<td>Division of New Drug Bioequivalence Evaluation (11/23/16)</td>
<td>Shila Nkah</td>
</tr>
<tr>
<td>Patient Labeling Review (4/27/17)</td>
<td>Shawna Hutchins, Puja Shah, Barbara Fuller, LaShawn Griffiths</td>
</tr>
<tr>
<td>Office of Prescription Drug Promotion (3/20/17)</td>
<td>Puja Shah</td>
</tr>
<tr>
<td>Division of Risk Management Reviews (6/2 and 9/1/17)</td>
<td>Jacqueline Sheppard, Theresa Ng, Joan Blair, Leah Hart, Jamie Wilkins</td>
</tr>
</tbody>
</table>

1. Introduction

On August 5, 2016, Actelion Pharmaceuticals Ltd. (Actelion) submitted NDA 209279 for Tracleer® (bosentan) dispersible tablets for the treatment of pulmonary arterial hypertension in adults and pediatric patients. The application references the applicant’s NDA for Tracleer® (bosentan) film coated tablets, which was approved in November 2001 for the treatment of pulmonary arterial hypertension.

The stated intent of the NDA is to:

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

Tracleer® (bosentan) is an oral endothelin receptor (ET\textsubscript{A} and ET\textsubscript{B}) antagonist approved in the U.S. in November 2001 as a treatment for PAH. Currently, Tracleer® (bosentan) film-coated tablets are approved in the U.S. for the following indication:

“Tracleer® is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with NYHA 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%)”\(^1\)

In the current NDA, the applicant seeks approval of a 32-mg dispersible tablet of bosentan for use in pediatric patients with PAH. The 32-mg dispersible tablet is currently approved in the European Union with dosing recommendations provided for pediatric PAH patients above 1 year of age.

As noted by the applicant, there are currently no approved therapies for the management of PAH in pediatric patients in the U.S. Because of bosentan’s orphan designation, Pediatric Research Equity Act (PREA) requirements do not apply. Products approved for the treatment of PAH in adults, including bosentan, are commonly used in the pediatric population.

The application is based on previously demonstrated efficacy in adults combined with hemodynamic, pharmacokinetic and safety data in pediatric patients with PAH using the marketed film-coated tablet and dispersible tablet formulation. The acceptability of such a submission, including the use of pulmonary vascular resistance (PVR) as an endpoint for establishing the effectiveness of bosentan in pediatric patients and the adequacy of the data supporting extrapolation of effectiveness from adults to pediatric patients, was discussed with Actelion at a meeting in July 2015. At that meeting, FDA indicated that, at least conceptually, it was open to the proposed approach. However, FDA also voiced a number of concerns about the ability of the data to support the proposed indication, including the lack of controlled efficacy and safety data in the pediatric population, the lack of long-term safety data in the pediatric population, and ethical concerns related to the appropriateness of using data that were obtained by methods (i.e., right heart catheterization in children) no longer considered ethical in clinical studies of pediatric PAH.

3. CMC

OPQ recommends approval of the application from a quality perspective. The dispersible tablet has a cross-shaped score originally intended to allow division of the tablet into half tablet parts as required by the applicant’s proposed dosing regimen for children. As discussed in the Quality Review,

\(^1\) The indication statement also contains the following “Considerations for use: “Patients with WHO Class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of hepatotoxicity in WHO Class II patients, which may preclude future use as their disease progresses.”
The applicant has agreed to a postmarketing commitment to change the cross-score to a single score to avoid medication errors.

**Drug substance:** Bosentan is a white to yellowish powder that is poorly soluble in water and in aqueous solutions at low pH. In the solid state, it is stable and neither hygroscopic nor light-sensitive. Bosentan belongs to a class of highly substituted pyrimidine derivatives, has no chiral centers, and is designated chemically as 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-[2,2´]-bipyrimidin-4-yl]- benzenesulfonamide monohydrate.

**Drug Product:** The drug product is a dispersible tablet that is quadrisected on one side and debossed with “32” on the other side. Each table contains 32 mg bosentan (in the form of 33.045 mg of bosentan monohydrate). Inactive ingredients include: cellulose microcrystalline, calcium hydrogen phosphate anhydrous, croscarmellose sodium, silica colloidal anhydrous, tartaric acid, tutti frutti flavor, aspartame (E951), acesulfame potassium, and magnesium stearate. Each dispersible tablet contains a small amount (1.87 mg) of phenylalanine.

**Expiration Date and Storage Conditions:** According to the Quality Assessment, the available stability data support the proposed 60-month shelf-life in the proposed commercial packaging (blisters composed of a bottom aluminum foil and a child-resistant push-through aluminum foil). The product should be stored at 20ºC – 25ºC (68ºF – 77ºF); these same conditions apply to the divided dispersible tablet, which may be returned to the opened blister and stored there for up to 7 days.

**Facilities review/inspection:** The office of Process and Facilities recommends overall approval for all of the currently listed manufacturing facilities. Manufacturing facilities were determined to be acceptable based on inspection history and review of establishment inspection reports.

**Notable issues during the review:**

As noted above, the proposed 32-mg dispersible tablet has a cross-shaped score to allow division of the tablet into half (16 mg) and thus enable the applicant’s proposed weight-based pediatric dosing. In tablet splitability studies, acceptable results for content uniformity were obtained for both manually and mechanically-split half-tablets. The revised dosing regimen proposed by the Office of Clinical Pharmacology and accepted by the applicant does not require quadrisection of the tablet to support pediatric dosing, thus providing a means to work around this issue. Because of concern that the cross-score may result in medication errors (see DMEPA reviews), the applicant will be given a postmarketing commitment to develop and submit data to support a change from cross- to single-scoring of the tablet. In the interim, the patient counseling information section of the label will also instruct providers to advise patients that the dispersible tablet should not be split into quarters.

### 4. Nonclinical Pharmacology/Toxicology

There are no barriers to approval from a pharmacology-toxicology perspective. Dr. Koerner’s review includes a brief discussion of the main findings in a juvenile toxicity study in rats, a study that Dr. Koerner initially reviewed in 2015. In this study, bosentan was administered to rats via oral gavage starting on postpartum day 4, and continuing through postpartum day 69, or through mating on postpartum day 84. According to Dr. Koerner’s review (text taken verbatim):

“Decreased body weights, absolute weights of testes and epididymides, and reduced number of...
sperm in epididymides were observed after weaning. No effect on testis histology or sperm morphology and function was seen. The NOAEL was 4 times (at Day 4 postpartum) and 2 times (Day 69 postpartum) the human therapeutic exposure, respectively. No effects on general development, sensory, cognitive function and reproductive performance were detected at the highest dose tested in juvenile rats, 7 times the therapeutic exposure in children with PAH.”

5. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology (OCP) recommends approval of the application from a clinical pharmacology perspective. The OCP review focused on the following issues:

• the bioavailability of the proposed bosentan oral dispersible tablet relative to the approved film coated tablet in healthy adults
• the pharmacokinetics of bosentan in pediatric patients relative to adult patients with PAH
• the pharmacokinetic bridge linking exposure from the proposed dosing regimen using dispersible tablets to the exposures achieved in the study supporting efficacy in children, in which the film-coated tablet was administered

As relates to these issues, the OCP review notes the following:

Relative Bioavailability: Relative to the 62.5-mg film-coated tablet, the dose corrected total systemic exposures (Cmax) and area under the plasma concentration-time curve (AUC0-∞) of the 32-mg dispersible tablet was slightly lower (geometric mean ratio 0.82 [90% CI: 0.65-1.04] and 0.87 [90% CI: 0.78-0.97], respectively). The OCP review notes that “For a chronic treatment such as bosentan, the total systemic exposure during the inter-dosing interval as reflected by AUC is likely to be more clinically relevant than Cmax” and concludes that the lower AUC is not likely to be clinically relevant based on the known pharmacokinetic variability of bosentan.

PK in pediatric patients: In pediatric patients with PAH aged 3 to 15 years administered the 31.25-, 62.5- or 125-mg film-coated tablets (dose approximately 2 mg/kg) twice daily, the average plasma exposure to bosentan at steady state was 37% lower than that observed in adult patients administered a 125-mg film-coated tablet twice daily. As also noted in the OCP review, following administration of a higher dose (4 mg/kg twice-daily) or a more frequent dosing regimen (2 mg/kg thrice-daily) to pediatric patients, mean systemic exposure to bosentan at steady state was similar to that observed at the 2-mg/kg dose, indicating that exposure to bosentan reaches a plateau at lower doses in pediatric patients than in adults and also that doses greater than 2 mg/kg/day in children are unlikely to result in greater exposures.

Bridging the proposed dosing regimen to the dosing regimen used in the study supporting pediatric efficacy: The film-coated tablet was used in the “pivotal” study supporting efficacy in children, BREATHE-3. According to the OCP review, the range of exposures achieved with a 2 mg/kg twice-daily dose of the dispersible tablet span the exposures achieved in BREATHE-3.

With regard to dosing, the applicant initially proposed a dose of 62.5 mg with uptitration to 125 mg after 4 weeks in patients >12 years old and >40 kg weight, a dose of 62.5 mg twice daily in patients <40 kg & >12 years of age, and a dose of twice daily in patients < 12 years of age. According to the OCP review, the submitted data support weight bands for dosing that would not require sectioning of the tablet into 4 parts. As noted in DMEPA’s review, these weight-based bands also resolve the concern that, even with
sectioning of the tablet the 32-mg tablet would not provide the complete dose range needed to achieve a dose of in patients.

6. Clinical/Statistical- Efficacy

In support of an indication in pediatric patients with PAH, Actelion provides analyses of data from ten completed studies in patients with PAH. This includes data from four completed studies in adults using the film-coated tablet and six completed studies in pediatric patients with PAH, five conducted with the dispersible tablet and one conducted with the film-coated tablet. An overview of the six completed pediatric studies is provided in the table below. Five of the six studies were uncontrolled single arm trials; one compared two dosing regimens. Two of the six trials were extensions to a parent trial and one of the trials was conducted in Japanese patients with PAH. With the exception of BREATHE-3, which used the film-coated tablet, all of the trials shown in the table below used the dispersible tablet.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population; number of subjects</th>
<th>Design</th>
<th>Objectives</th>
</tr>
</thead>
</table>
| AC-052-356       | 3-15 years; WHO FC II or III PPH or associated PAH-CHD; n=19 | Open-label, single-arm, uncontrolled 12-week study | Primary objective: PK  
Secondary objective: Efficacy, hemodynamics and safety          |
| (BREATHE-3)      |                                 |                                              |                                                                   |
| AC-052-365       | ≥ 2 and < 12 years; WHO FC II or III IPAH or familial PAH; n=36 | Open-label, single-arm, uncontrolled 12-week study | Primary objective: To demonstrate that exposure to bosentan in children with PAH (dispersible tablet) is similar to that in adults with PAH (film-coated tablet)  
Secondary objective: Safety and tolerability                |
| (FUTURE 1)      |                                 |                                              |                                                                   |
| AC-052-367       | Patients from FUTURE 1; n=33   | Open-label, uncontrolled extension to FUTURE 1 | Primary objective: Long-term safety  
Secondary objective: Efficacy                                    |
| (FUTURE 2)      |                                 |                                              |                                                                   |
| AC-052-373       | ≥ 3 months and < 12 years; WHO FC I, II or III IPAH, heritable PAH, or associated PAH-CHD; n=64 | Open-label, randomized trial comparing two dosing regimens (2 mg/kg bid and 2 mg/kg tid) | Primary objective: To investigate the PK of the dispersible tablets of bosentan at doses of 2 mg/kg b.i.d. and 2 mg/kg t.i.d.  
Secondary objectives: Efficacy and safety                |
| (FUTURE 3)      |                                 |                                              |                                                                   |
| AC-052-374       | Patients from FUTURE 3; n=58   | Open-label, randomized, two-dose regimen extension to FUTURE 3 | Primary objective: Long-term safety, tolerability  
Secondary objective: Efficacy                                  |
| (FUTURE 3 extension) |                              |                                              |                                                                   |
| AC-052-377       | Japanese patients ≥ 1 year and < 14 years with WHO FC II, III or IV IPAH, heritable PAH, or associated PAH-CHD; n=6 | Open-label, single-arm, uncontrolled 12-week study | Primary objective: To evaluate the effect of bosentan on PVR  
Secondary objectives: Effects on other hemodynamic variables, WHO FC, PK, safety and tolerability |
|                  |                                 |                                              |                                                                   |
The efficacy evaluation relies on the findings in one of these trials—BREATHE-3, an open-label, uncontrolled study in 19 pediatric patients with PAH aged 3 to 15 years. This study’s findings of a reduction in pulmonary vascular resistance (PVR) were used to bridge the bosentan efficacy findings in adults to pediatric patients with PAH. The reviews by Dr. Zhang (Statistical Review) and Drs. Garnett and Florian (Clinical and Clinical Pharmacology Efficacy Review) explore whether such an approach is supported.

To address this issue, Drs. Garnett and Florian undertook analyses exploring the following questions:

1. Can the relationship between the change in PVR and change in 6-minute walk distance (6MWD) developed using data from intervention trials in adult patients with PAH be used to extrapolate efficacy to pediatric patients?
2. Do pediatric patients with PAH achieve a sufficient decrease in PVR with bosentan treatment to establish clinical efficacy?

As a first step, Drs. Garnett and Florian analyzed data from 12 randomized, double-blinded, placebo-controlled trials that collected information on PVR and 6MWD in adults with PAH (totaling 2028 subjects and 9 drugs). Analyses of these data show a relationship between improvement in 6MWD and a decrease in PVR using pooled patient-level data for active and placebo treatments that appears to be consistent across drug classes and individual drugs (see Figure below and also Figures 2-5 of their review).

**Figure 1: Relationship between change in PVR and change in 6MWD by Treatment Assignment**
Source: Figure 1, Clinical and Clinical Pharmacology Efficacy Review

*Shown are the observed data by treatment assignment overlaid with regression slope and 95% confidence interval. Black error bars represent mean and standard deviation Δ6MWD within each decile of ΔPVR.*
Next, the reviewers used patient-level data from three randomized, placebo-controlled trials of bosentan in adults to evaluate how much of the treatment effect of bosentan in these trials could be explained by the treatment effect on PVR. Using their analytic approach, approximately 49% of bosentan’s treatment effect on 6MWD in these trials could be explained by the change in PVR.

The reviewers then turned to the size of the treatment effect on PVR observed in BREATHE-3, which collected data on changes in PVR in pediatric patients treated with bosentan. According to their analyses, the mean change in PVR in BREATHE-3 was similar to the mean change in adult PAH patients treated with bosentan and decreased relative to the mean change in adult PAH patients receiving placebo and pediatric PAH patients receiving placebo (see figure and table below).

![Box plot showing the mean (white circles), median (notch), 95% CI of median (width of notch), 25th and 75th percentile (with of box), 1.5*IQR range (whiskers), and outliers (filled circles).](attached_image)

**Figure 2: Distribution of change in PVR in Pediatric and Adult Patients with PAH**

Source: Figure 10, Clinical and Clinical Pharmacology Efficacy Review
Finally, the reviewers performed stochastic simulations using the regression model in adults to assess whether the change in PVR observed in BREATHE-3 would result in increases in 6MWD that excluded zero. Their results, shown in Table 14 of their review, appear to indicate that the observed mean decrease in PVR in pediatric patients treated with bosentan in BREATHE-3 would be expected to result in an improvement in 6MWD/exercise ability.

Based on the aforementioned findings, Drs. Garnett and Florian conclude that the PVR data from BREATHE-3 support the clinical efficacy of bosentan in pediatric patients with PAH.

In her statistical review, Dr. Zhang addresses a somewhat different question: whether bosentan would have shown a significant treatment effect on 6MWD if there had been a placebo arm and 6MWD had been measured in BREATHE-3. To approach this issue, Dr. Zhang first applies a bivariate fixed-effects model to the three randomized, placebo-controlled trials of bosentan in adults to estimate the overall relationship between PVR and 6MWD. According to Dr. Zhang, the individual-level and trial level $R^2$ values—0.37 and 0.65, respectively, indicate that “PVR may not be considered a reliable surrogate for 6MWD in the bosentan adult trials.”

Next, Dr. Zhang applies bootstrapping to generate PVR data for a putative placebo arm using the PVR data from the placebo arm in a pediatric trial (the same trial used by Drs. Garnett and Florian). According to Dr. Zhang, her simulations show that (1) there is only at most a 50% chance of demonstrating a significant treatment effect of bosentan on PVR with a sample size of 17 in each treatment arm, and (2) bosentan’s effect on 6MWD relative to a putative placebo is predicted to be ~60 meters with a 95% prediction interval that overlaps with zero (-26, 145).

Dr. Zhang concludes her review by noting that she is not able to predict that bosentan would have demonstrated a statistically significant treatment effect on 6MWD, had BREATHE-3 had a placebo arm of similar sample size to the arm that received open label bosentan treatment in BREATHE-3 and had 6MWD been measured in the trial. She is otherwise silent on whether the product should be approved for the treatment of pediatric patients with PAH.

In her Clinical Review, Dr. Gordon discusses the PVR findings in BREATHE-3, as well as changes in WHO functional class and Global Clinical Impression (GCI) Scale and the incidence of PAH worsening in FUTURE 1 and 2, and in FUTURE 3 and its extension trial. The applicant cites

---

### Table 1: Summary of change in PVR in Adults and Pediatric Patients

<table>
<thead>
<tr>
<th>ΔPVR, dyn.sec/cm²</th>
<th>Pediatrics</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bosentan</td>
<td>Placebo</td>
</tr>
<tr>
<td>N</td>
<td>17</td>
<td>50</td>
</tr>
<tr>
<td>Mean</td>
<td>-389</td>
<td>6.3</td>
</tr>
<tr>
<td>Median</td>
<td>-266</td>
<td>-8.5</td>
</tr>
<tr>
<td>SD</td>
<td>616</td>
<td>944</td>
</tr>
<tr>
<td>95% CI</td>
<td>-682, -96</td>
<td>-255, 268</td>
</tr>
</tbody>
</table>

*Data were obtained from AC-052-356 (bosentan pediatric), A1481131 (placebo pediatric), and pooled studies in adults (Table 6). Abbreviations: Δ change from baseline; PVR, pulmonary vascular resistance; SD, standard deviation; N, number of subjects; CI, confidence interval. Source: EfficacyJmd*
the low rate of disease deterioration, demonstrated by stable WHO FC status over a 3-month
treatment duration across adult and pediatric studies as support for efficacy; however given that the
“usual course of disease” as assessed using WHO FC does not appear to be highly predictable and
the lack of a control arm in these trials, the findings are difficult to interpret. The same can be said
of the CGI Scale and PAH worsening analyses. Dr. Gordon concludes that: “Bosentan should not
be approved for use in children with PAH because there is no demonstration of clinical benefit in
adequate and well controlled trials. All efficacy trials for this indication were uncontrolled. While
there were changes in cardiac hemodynamics generally viewed as improvements, these changes
are insufficient to be used as proof of efficacy for any PAH drug, especially the first one to have
such an indication.”

7. Safety

While support for efficacy is provided in large part by BREATHE-3, which studied a 2-mg/kg
dose of the film coated tablet, safety analyses focused on a pooled dataset containing data from
100 pediatric patients, ranging in age from 3 months to 12 years, treated in Future 1 and Future 3
and their extension studies, in which subjects were administered the dispersible tablet.

According to Dr. Gordon’s review, the mean and median duration of exposure in the pooled safety
dataset was 21 and 17 months, respectively (range of 0.1 to 59 months) and a total of 77 subjects
were exposed for at least one year. The mean and median age of subjects in the pooled dataset
were ~5 years; of the 100 subjects, 21 were less than 2 years of age. Of the patients enrolled in
these studies, 91% were enrolled at sites outside the US.

As discussed in Dr. Gordon’s review, based on the experience in adults and the larger experience
with the pharmacologic class, safety topics of interest included anemia, liver toxicity, and edema.
Interpretation of the safety database as relates to these potential toxicities is somewhat limited
because of the lack of a control arm and because these events can also reflect disease worsening.
Nevertheless, the available data from the clinical trials suggest a safety profile similar to that
observed in adults.

- With regard to the risk of liver toxicity, in the pooled dataset, elevations in liver
aminotransferases ≥ 3 × ULN were observed in 2% of patients and no subject experienced
an increase aminotransferases ≥ 3 × ULN in combination with an increase in total bilirubin
> 2x ULN.
- Of the subjects included in the pooled safety dataset, a decrease in hemoglobin levels to <
10 g/dL from baseline was reported in 11% of patients, whereas a decrease to < 8 g/dL was
not reported in any subject. In her review, Dr. Gordon describes the decreases as mild and
notes that they rarely required intervention.
- Of the 100 subjects included in the pooled dataset, eighteen (18%) were reported to have
an AE leading to drug discontinuation, a finding that is difficult to interpret in isolation
(i.e., in the absence of a placebo-control).

Dr. Gordon’s review also contains a discussion of the pediatric post-marketing experience, which,
as noted by Dr. Gordon, does not raise additional concerns.

8. Advisory Committee Meeting
No Advisory Committee Meeting was held. The use of PVR to “bridge” the efficacy findings in adults to pediatric patients with PAH was previously discussed at a Cardiovascular and Renal Drugs Advisory Committee meeting on July 29, 2010, at which time the data on this topic were less complete than they now are. At the conclusion of the discussion, the committee was asked to vote on the following question: “Does the Committee agree that, for a product with an approved indication in adults with PAH, a treatment effect on PVRI can be used to demonstrate effectiveness and to derive dosing information in the pediatric PAH population?” The vote was split, with seven committee members voting “yes” and six voting “no”.

9. Pediatrics

See discussions in other sections of the review.

10. Other Relevant Regulatory Issues

**Ethics:** The Office of Pediatric Therapeutics was consulted regarding ethical questions related to the use of data collected through right heart catheterization (RHC) as an outcome measure in pediatric studies, and specifically the ethics of reliance upon PVR data from BREATHE-3 to support approval. In her review, Dr. Snyder argues that, from an ethical perspective, the RHC data from BREATHE-3 may be used to support the application, citing the following rationale: “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 in the sildenafil trials 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.”

**Inspections:** As discussed in OSI’s Clinical Inspection Summary, one domestic site clinical investigator (Dunbar Ivy, Colorado) was inspected in support of NDA 209279. This site was one of two sites that enrolled subjects in Study AC-052-356 (BREATHE-3), the pivotal study supporting efficacy. Although regulatory violations were found during the inspection, OSI believes that the violations that were identified are unlikely to have impacted the study outcome or reliability of the data submitted in support of approval. Hence, OSI recommends that the data submitted by the applicant from this site be accepted. Based on my review of OSI’s Clinical Inspection Summary, I agree with their assessment of the violations.

**REMS:** The currently marketed formulation of Tracleer (bosentan, film-coated tablets) has a REMS that includes a medication guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments. The 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 has reviewed the REMS document and supporting materials submitted by Actelion Pharmaceuticals and provided recommended edits. At this time, there are no outstanding issues with the REMS.
11. Labeling

At this time, agreement has been reached on labeling, including the prescriber information, medication guide, cartoon labels, and container labels. As discussed in the DMEPA reviews, the applicant was instructed to revise the proposed commercial packaging (blister packs) 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. The applicant has made these revisions, but notes that readability (which, according to the applicant may be an issue given the size of the bar codes), cannot be confirmed prior to approval. Actelion has agreed to inform FDA of the results once available and has also committed to take immediate action to develop larger blister packaging that can accommodate larger, readable bar codes if they receive customer post-market complaints about the ability to scan the blister label bar codes. Both DMEPA and DCRP agree that the proposed plan is acceptable. Given the Agency’s experience with other products, it is thought that readability is unlikely to be an issue.

Proprietary name: According to DMEPA, the proposed proprietary name, Tracleer, is acceptable.

12. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

Approval for the following indications: Tracleer® is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in:

- adults to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness in adults included predominantly patients with WHO 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%)
- pediatric patients aged 3 years and older with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability

Risk Benefit Assessment

Tracleer® (bosentan) is an oral endothelin receptor (ETA and ETB) antagonist approved in the U.S. for the treatment of PAH (WHO Group 1) to improve exercise ability and to decrease clinical worsening in adults. In the current NDA, the applicant seeks approval of a 32-mg dispersible tablet of bosentan for use in pediatric patients with PAH. In support of such a claim, Actelion provides analyses of data from ten completed studies in patients with PAH. The efficacy evaluation relies on the findings in one of these trials—BREATHE-3, an open-label, uncontrolled study in 19 pediatric patients with PAH aged 3 to 15 years. This study’s findings of a reduction in pulmonary vascular resistance (PVR) were used to bridge the bosentan efficacy findings in adults to pediatric patients with PAH.

Dr. Gordon, the clinical reviewer, recommends against approval for the proposed pediatric indication, citing insufficient evidence of effectiveness. Her concern appears to stem from the use of a bridging biomarker and the absence of a concurrent control in the pediatric trials submitted in...
support of approval. We agree that the data on WHO functional class and Global Clinical Impression (GCI) Scale and the incidence of PAH worsening in FUTURE 1 and 2, and in FUTURE 3 and its extension trial are difficult to interpret given the lack of a control arm. However, we think baseline controlled data on PVR are interpretable, because, given the natural history of the disease, significant improvements in PVR would not be expected absent an intervention.

Arguably, the case for PVR to be considered a surrogate for exercise is fairly compelling. PVR is plausibly on the causal pathway in WHO Group 1 disease. All approved therapies are non-specific vasodilators, and one can account for some portion of the variability in response on 6-minute walk distance (6MWD) within a development program and across development programs with observed changes in PVR. PVR does not account for all of the variability in 6MWD in adults, probably in part because of noise in measurements of both 6MWD and PVR that has nothing to do with intrinsic hemodynamics or exercise capacity. Although the Agency has not concluded that showing an effect on PVR suffices to approve a novel agent for PAH, its use to infer benefit of an approved agent in pediatric patients is reasonable and, one could argue, a relatively small step.

Generally speaking, certain criteria should be satisfied if a bridging biomarker is to be used to infer benefit in pediatric patients with PAH. Specifically, the forms of PAH studied in adults and children should be sufficiently similar to allow borrowing of information from the development program in adults. Data should also indicate that (1) the bridging biomarker can be relied upon to predict efficacy in pediatric patients and (2) the size of the treatment effect on the bridging biomarker in pediatric patients is sufficiently large that the observed effect on the bridging biomarker would be expected to translate into a clinical benefit.

As relates to these issues, the analyses conducted by Drs. Garnett and Florian confirm: (1) that the relationship between improvements in 6MWD and PVR in adults is relatively consistent across drug classes and drugs; and (2) that the treatment effect of bosentan on PVR in adults accounts for a reasonable fraction of the treatment effect of bosentan on 6MWD in adults, considering the likely intrinsic variability of these data. Their analyses also suggest that the size of the treatment effect on PVR in pediatric patients treated with bosentan in BREATH-3 would be expected to result in an improvement in 6MWD. (Indeed, the nominal effect on PVR—even uncorrected for body surface area—is larger in pediatric patients that it was in adults.) We believe these findings support the conclusion that in pediatric patients aged 3 years and older (i.e., the age ranges of patients included in BREATH-3) with idiopathic or congenital PAH, bosentan improves PVR and that this improvement would be expected to result in an improvement in 6MWD/exercise ability.

In her review, Dr. Zhang states that she was unable to predict that bosentan would have demonstrated a statistically significant treatment effect on 6MWD, had BREATH-3 had a placebo arm of similar sample size to the arm that received open label bosentan treatment in BREATH-3 and had 6MWD been measured in the trial. While this may be true, we do not think that this issue (i.e., whether a study the size of BREATH-3 would have shown a statistically significant effect on 6MWD) is the key issue. Hence, Dr. Zhang’s analyses do not alter our conclusion.

With regard to safety, the submitted safety database, which includes findings from uncontrolled trials and data on the postmarketing experience, allow one to assess (1) whether bosentan’s safety profile in the target pediatric population is grossly similar to that seen in the clinical trials that supported approval in adults and (2) whether toxicities identified in adults occur in a more severe
form or at a marked increase in rate in pediatric patients. The submitted data suggest that the safety profile of bosentan in pediatric patients is grossly similar to that in adults and do not suggest that the previously identified toxicities in adults occur in a more severe form or at a marked increase in rate in pediatric patients.

In closing, we believe the evidence supports the approval of bosentan for the treatment of pediatric patients with idiopathic or congenital PAH. Labeling should also be transparent about the basis for concluding benefit. In this regard, labeling should indicate that bosentan is indicated in this population to improve PVR, which is expected to result in an improvement in exercise ability.

**Recommendation for Postmarketing Risk Evaluation and Management Strategies**

The currently marketed formulation of Tracleer (bosentan, film-coated tablets) has a REMS that includes a medication guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments. The 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 agree that a REMS is necessary to ensure the benefits outweigh the risks for bosentan dispersible tablets for the proposed indication.

**Recommendation for other Postmarketing Requirements and Commitments**

The applicant has agreed to a postmarketing commitment to develop and submit CMC information supporting a change to the scoring of the tablet, i.e. changing the cross-score to a single score.

**Recommended Comments to Applicant**

None at this time.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALIZA M THOMPSON
09/04/2017

NORMAN L STOCKBRIDGE
09/04/2017
I concur with all aspects of this review.