CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209279Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 209279; Tracleer® (Bosentan) Tablets for Oral Suspension

Integrated Quality Review

Recommendation: Approval

Drug Name/Dosage Form	Tracleer® (Bosentan) Tablets for Oral Suspension
Strength	Each tablet contains 32 mg of bosentan
Route of Administration	Tablets for oral use
Rx/OTC Dispensed	Rx
Applicant	Actelion Pharmaceuticals Ltd.
US agent, if applicable	

Submissions (s) Reviewed	NDA 209279, and all the submitted CMC amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance and Drug Product	Stephanie Emory	ONDP/DNDPI/NDPBI
Process	Peter Guerreier	OPQ/OPF/DPAI/PABI
Facility	Zhong Li	OPF/DIA/IABI
Biopharmaceutics	Joan Zhao	ONDP/DB/BBI
Regulatory Business Process Manager	Dahlia Woody	OPRO DRBPMI/RBPMBI
Environmental Assessment (EA)	Stephanie Emory	ONDP/DNDPI/NDPBI
Laboratory (OTR)	N/A	
Application Technical Lead	Mohan Sapru	ONDP/DNDPI/NDPBI

1. RELATED/SUPPORTING DOCUMENTS:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	058317	Initial studies concerning the use of bosentan in patients with pulmonary arterial hypertension
NDA	021290	Approved use of Tracleer (bosentan) film-coated tablets in patients with pulmonary arterial hypertension
pNDA Meeting Minutes, August 10, 2015		pIND meeting package to support the pediatric use of Tracleer using an appropriate pediatric formulation
DMF	# (b) (4)	Previously reviewed and found adequate.

2. CONSULTS: N/A

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls (CMC) perspective, NDA 209279 (Tracleer® (Bosentan) Tablets for Oral Suspension) is recommended for approval.

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

Given that the revised dosing instructions eliminate the need for using any split quarter tablets, a PMC is required to change the cross-score (indicating a quadrisected tablet) to a single score tablet. Removal of the non-functional scoring via this PMS is aimed to avoid patient confusion that may result in incorrect dosing of pediatric patients. As part of the PMC, the applicant needs to submit appropriate CMC information supporting the change from double scored (quadrisected tablet) to to a single scored tablet, such as:

- Plan for switching from quadrisected to bisected product on the market and educating physicians and patients about the change in product appearance
- Plan for submission of CMC CBE-30 supplement to the approved NDA
- Descriptions of all changes made to the product
- Comparative release and stability data to confirm no impact to performance or quality
- Half-tablet breakability and in-use stability studies, as appropriate
- Updated product labeling, as needed

II. Summary of Quality Assessments

Tracleer® (Bosentan; 62.5 mg and 125 mg film-coated tablets for oral administration) was originally approved in 2001 in the US (NDA 021290) for the treatment of pulmonary arterial hypertension (PAH). The applicant, Actelion Pharmaceuticals Ltd., has sought U.S. marketing approval for Tracleer® (Bosentan) Tablets for Oral Suspension under the provisions of Section 505(b)(1) of the Federal Food and Cosmetic Act and 21 CFR §314.50. This submission references IND 058317 and NDA 021290 for the use of bosentan in patients with pulmonary arterial hypertension (PAH). Specifically, this NDA seeks approval for the use of Tracleer® for the treatment of pediatric patients (<12 years of age) with pulmonary arterial hypertension (PAH) using a new scored 32 mg dispersible tablet presentation of Tracleer. The efficacy evaluation in this NDA is based on the 'bridging' of data between the adult and pediatric studies primarily utilizing the pivotal, Phase 3 trial, AC-052-356, in which both adult and pediatric patients were dosed with 62.5 mg and 125 mg bosentan film-coated tablets.

A. \Drug Substance (Bosentan) Quality Summary

Tracleer is the proprietary name for bosentan, an endothelin receptor antagonist i.e., a specific and competitive antagonist at endothelin receptor types ET_A and ET_B. It belongs to a class of highly substituted pyrimidine derivatives, with 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. Bosentan, in the solid state, is very stable, is not hygroscopic or light sensitive. The drug substance has been previously reviewed under NDA 021290.

B. Drug Product (Bosentan Tablets for Oral Suspension) Quality Summary

The drug product consists of clover-shaped dispersible tablets that are quadrisected on one side, debossed with "32" on the other side, and contain 32 mg bosentan (in the form of 33.045 mg of bosentan monohydrate). No novel or animal/human-original excipients are used. All excipients are compendial or below the levels for previously approved products except Tutti Frutti flavor (referenced to DMF (b) (4)). DMF (b) (4)) has been reviewed previously and found adequate for ANDA 78-367 Desloratadine orally disintegrating tablets (reviewed by G. Kang, 2006).

Content Uniformity: The original aim of the pharmaceutical development was to develop a new form of bosentan drug product i.e., a 32 mg of bosentan-containing quadrisected dispersible tablet that can be dispersed in (b) (4) water for pediatric use. Because the amount of active pharmaceutical ingredient is less than (b) (4)% of the total mass, uniformity of dosage unit has been confirmed by testing content uniformity per Ph. Eur. 2.9.40, which is comparable to USP <905>according to ICH Q4B Annex 6. (b) (4) the applicant carried out tablet splitability studies using half-tablets, which involved using both manual and mechanical splitting approaches. Acceptable results for content uniformity (by HPLC) have been obtained for both manually- (b) (4) and mechanically-split (b) (4) half-tablets. The highest and lowest values have been found to be within the USP limits for split tablets using either of these splitting methods. However, manual splitting resulted in significantly better content uniformity and lower loss of mass compared to the mechanical splitting. Friability appears largely unaffected by splitting method except at low hardness. Hence

from product quality perspective, the use of manually split half tablets (b) (4) is acceptable. Hence, as per the revised dosing instructions, division into quarter-tablet parts is no longer needed. The applicant has been advised to remove the nonfunctional score in order to avoid patient confusion and unintended tablet division into quarter-tablet parts.

Manufacturing: The proposed manufacture of bosentan dispersible tablets (b) (4)

Microbiological Aspects: Bosentan is a dry dosage form for oral administration and does not contain antimicrobial preservatives. Neither bosentan drug substance nor the excipients have inherent antimicrobial activity. Therefore, as recommended by the Decision tree #8 of the ICH guideline Q6A, microbial limits have been established according to the harmonized pharmacopoeial monograph described in the ICH Harmonized Tripartite Guidelines Q4B annex 4C(R1) "Microbiological examination of non-sterile products: acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use. The microbial quality has been checked during long-term stability in the commercial packaging configurations on clinical batches. Based upon 60 months of data, all results comply with the specifications.

Biopharmaceutics Aspects: In view of ICH Q6A guidelines, the applicant's initial proposal of using (b) (4) in lieu of dissolution testing was not acceptable. Recently, the applicant provided dissolution data on half tables (using both non-mechanical and mechanical splitting), to support the use of tablets split into two halves as per the revised dosing instructions. Based on dissolution data provided, the following revised dissolution method and acceptance criterion are acceptable and agreed upon:
Apparatus USP II (Paddle); Rotation Speed 75 RPM; Medium 1M HCl pH 1.1 with 0.5% SDS; Volume 900 mL; Acceptance Criterion Q= (b) (4)% in 15 minutes.

Control Strategies: The product control strategies mainly consist of in-process controls, and release-, and stability testing. (b) (4)

Container Closure System: The dispersible tablets will be commercially available in Alu / Alu blisters composed of a blister pack bottom foil and a child-resistant push-through foil. This packaging material offers adequate protection for maintaining the integrity of the finished product.

Expiration Date & Storage Conditions: Based on product stability data, including the in-use stability data, the Agency approves a shelf-life of 60 months for the product when stored in the approved commercial container closure system at controlled room temperature i.e., 20°C - 25°C (68°F – 77°F). The divided tablets, stored 20°C - 25°C (68°F – 77°F), should be used within 7 days of having been broken. Tablet pieces may be returned to the opened blister and stored there out of reach of children for up to 7 days.

C. Assessment of Manufacturing Facilities: The office of Process and Facilities has recommended overall approval for all the currently listed manufacturing facilities concerning this NDA. Both facility and process risks have been deemed low and the initially identified process risk has been mitigated.

III. Summary of Drug Product and Intended Use

Proprietary Name of the Drug Product	Tracleer
Non Proprietary Name of the Drug Product	Bosentan tablets for oral suspension
Active ingredient	Bosentan

Proposed Indication(s) including Intended Patient Population	Tracleer is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (WHO Group 1): The product carries warning about risks of hepatotoxicity and embryo-fetal toxicity.
Methods of Administration	Tracleer film-coated tablets and tablets for oral suspension (dispersible tablets) should be administered orally twice daily. Disperse the tablets for oral suspension, or the half tablet in a minimal amount of water immediately before administration
Maximum Daily Dose/ Duration of Treatment	Patients >12 years of age and >40 kg 62.5 mg twice daily (Initial 4 weeks) 125 mg twice daily (after 4 weeks) Patients >12 years of age and <40 kg 62.5 mg twice daily Patients ≤12 years of age ≥4-8 kg: 16 mg twice daily >8-16 kg: 32 mg twice daily >16-24 kg: 48 mg twice daily >24-40 kg: 64 mg twice daily
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Designation: The Sponsor did not request an official BCS designation. Bosentan, a BCS class-II moiety, possesses moderate to high permeability, and low solubility.
2. Biowaivers/Biostudies: A biowaiver is not requested nor required for this NDA.
3. IVIVC: N/A.

E. Any Special Product Quality Labeling Recommendations: N/A

F. Life Cycle Knowledge Information

See Final Risk Assessment on the next page.

Final Risk Assessment-

NDA 209279 - Tracleer® (Bosentan) Tablets for Oral Suspension

Attribute/ CQA	Factors Impacting CQAs	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
Assay, Stability	• Formulation • Container closure • Impurity exceeding specification • Process parameters • Scale/ equipment/ site	Low (L)	The product CQAs such as identification, assay, and impurity levels are controlled by appropriate release specification using validated analytical methods. Product stability for a period of 60 months at controlled room temperature conditions has been demonstrated	Acceptable	Changes in packaging configuration should be closely evaluated , especially if it is changed from alu/alu blister packaging to more moisture-permeable components such as plastics/polymers
Solid state Polymorphic form)	• Formulation • Raw materials • Process parameters • Scale/ equipment/ site	Mode-rate (M)	In the solid state, bosentan is very stable, is not hygroscopic and is not light sensitive. Bosentan is a previously approved API	Acceptable	N/A
Content Uniformity	• Formulation • Particle size • Segregation • Raw materials • Process parameters • Scale/ equipment/ site	Moder-ate (M)	Given that the amount of active pharmaceutical ingredient is less than (b)(4)% of the total mass, uniformity of dosage unit is confirmed by content uniformity release testing per USP <905>	Acceptable	Any proposed changes to formulation, manufacturing or the control strategy will need to be evaluated for possible impact on content uniformity

Attribute/ CQA	Factors Impacting CQAs	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
Functionally scored tablets: content uniformity (b) (4)	• Formulation • (b) (4) • Raw materials • Process parameters • Scale/equipment/site	Moder-ate (M)	Acceptable results for content uniformity (by HPLC) for both manually- (AV=4) and mechanically-split (AV=14) half-tablets have been provided	Acceptable	(b) (4)
Functionally Scored Tablets: Friability	• Formulation • Process parameters Scale/equipment/site	Low (L)	The tablet friability is monitored according to Ph. Eur. 2.9.7. , which is interchangeable with USP <1216>	Acceptable	Any proposed CMC changes with potential for impact on tablet hardness should be scrutinized.
Dissolution – BCS Class II & IV	• Formulation • Raw materials • Process parameters Scale/equipment/site	Moder-ate (M)	The revised dissolution method and acceptance criterion are adequate for monitoring product dissolution on release	Acceptable	
Functionally Scored Tablets: Dissolution	• Formulation • Raw materials • Process parameters Scale/equipment/site	Moder-ate (M)	The applicant provided dissolution data on half tables obtained by both non-mechanically and mechanically splitting to support the functional score of the proposed tablets	Acceptable	Any proposed changes to formulation, manufacturing or the control strategy will need to be evaluated for possible impact on content uniformity of split tablets
Microbial limits	• Formulation • Raw materials • Process parameters Scale/equipment/site	Low (L)	The microbial quality of the product is tested on release according to Ph. Eur. 2.9.12	Acceptable	

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead (ATL) Assessment and Signature:

From the chemistry, manufacturing, and controls (CMC) perspective, NDA 209279 (Tracleer® (Bosentan) Tablets for Oral Suspension) is recommended for approval.

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead for Cardiovascular and Renal Products (Acting)
ONDP/DNDPI/NDPBI

Mohan K. Sapru -S

Digitally signed by Mohan K. Sapru -S
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LABELING

R Regional Information

1.14 Labeling

Prescribing Information *- date of last update: 06Jun2017. Labeling for the tablets for oral suspension will be incorporated into the existing PI for the Tracleer film-coated tablets (62.5 mg and 125 mg).*

1. "Highlights" Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	TRACLEER® (bosentan)	Adequate
Dosage form, route of administration	tablets for oral suspension	Adequate
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Tablet for oral suspension: 32 mg	Adequate.

Reviewer's Overall Assessment: Adequate.

2. "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	32 mg tablets for oral suspension	Adequate.
Strengths: in metric system	See "Available Dosage Forms"	Adequate.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	632 mg tablets for oral suspension: clover-shaped, quadrisected, pale yellow to off-white tablets, debossed with identification marking "32" on the side opposite the quadrisection lines.	Adequate.

Reviewer's Overall Assessment: Adequate.

 # 5: Warnings and Precautions

Item	Information Provided in NDA	Reviewer's Assessment
Phenylketonurics caution statement	(b) (4) (b) (4) Tracleer dispersable tablets contain phenylalanine, a component of aspartame. Each dispersible tablet contains 1.87 mg of phenylalanine. (b) (4)	Correct spelling of "dispersible." The quantity of phenylalanine is consistent across all labels and labeling.

Reviewer's Overall Assessment: Adequate, pending applicant's acceptance of the change noted above.

#11: Description (21CFR 201.57(c)(12))

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Tracleer is the proprietary name for bosentan...	Adequate
Dosage form and route of administration	Tracleer is also available as a 32 mg tablet for oral suspension...	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	Each dispersible tablet contains 33.045 mg of bosentan monohydrate, equivalent to 32 mg anhydrous bosentan.	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Tracleer is also available as a 32 mg tablet for oral suspension and contains the following excipients: cellulose microcrystalline, calcium hydrogen phosphate anhydrous, croscarmellose sodium, silica colloidal anhydrous, tartaric acid, tutti frutti flavor, aspartame (E951) (b) (4), acesulfame potassium, and magnesium stearate.	• Replace "cellulose microcrystalline" with "microcrystalline cellulose." • Replace "calcium hydrogen phosphate anhydrous" with "dibasic calcium phosphate." • Replace "silica colloidal anhydrous" with "colloidal silicon dioxide." • List excipients in alphabetical order.

#11: Description (21CFR 201.57(c)(12)) - continued

Item	Information Provided in NDA	Reviewer's Assessment
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	an endothelin receptor antagonist that belongs to a class of highly substituted pyrimidine derivatives	Adequate.
Chemical name, structural formula, molecular weight	Chemical name: 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-[2,2´]-bipyrimidin-4-yl]-benzenesulfonamide monohydrate Empirical formula: $C_{27}H_{29}N_5O_6S \bullet H_2O$ Molecular weight: 569.64	Adequate. The chemical structure in the figure provided is accurate.
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	No chiral centers Bosentan is a white to yellowish powder. It is poorly soluble in water (1.0 mg/100 mL) and in aqueous solutions at low pH (0.1 mg/100 mL at pH 1.1 and 4.0; 0.2 mg/100 mL at pH 5.0). Solubility increases at higher pH values (43 mg/100 mL at pH 7.5). In the solid state, bosentan is very stable, is not hygroscopic and is not light sensitive.	Adequate.

Reviewer's Overall Assessment: Adequate, pending the applicant's acceptance of the changes noted above.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	32 mg tablets for oral suspension	Adequate
Available units (e.g., bottles of 100 tablets)	NDC 66215-103-56: Carton of 56 tablets for oral suspension in 4 blister-strips of 14 tablets. NDC 66215-103-14: Blister strip of 14 tablets for oral suspension.	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	32 mg tablets for oral suspension, pale yellow to off-white, clover-shaped, quadrisected on one side and debossed with "32" on the other side, packaged in child resistant Aluminum/Aluminum peel-push blisters.	Adequate (see "Available units" for NDC #)
Special handling (e.g., protect from light, do not freeze)	None stated.	Adequate
Storage conditions	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 dispersible tablets. Divided dispersible tablets should be stored under the same conditions 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.	Adequate

Reviewer's Overall Assessment: Adequate.

#17: Patient Counseling Information

Item	Information Provided in NDA	Reviewer's Assessment
Tablet division instructions	Administration Considerations Advise patients that Tracleer dispersible tablets should not be split into quarters.	Adequate.

Reviewer's Overall Assessment: Adequate.

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	At the end of Section (b)(4): Manufactured for: Actelion Pharmaceuticals US, Inc. South San Francisco, CA 94080, USA	Relocate to follow section 17

Reviewer's Overall Assessment: Adequate, pending the applicant's acceptance of the change noted above.

Medication Guide

Item	Information Provided in NDA	Reviewer's Assessment
Phenyl-ketonurics caution statement	Tracleer 32 mg dispersible tablets contain Aspartame. Phenylketonurics: Contains Phenylalanine 1.87 mg per 32 mg dispersible tablet.	Adequate.
Tablet division instructions	If necessary, the 32 mg dispersible tablet can be divided into halves by breaking along the lines cut into the surface. Hold the tablet between the thumb and index finger on either side of one of the lines, with the line facing upwards, and break the tablet along the line (see figure below). The dispersible tablet should not be broken into quarters.	Adequate. The figure provided matches the instructions.
Storage conditions	Store Tracleer at room temperature between 68°F to 77°F (20°C to 25°C). Dispersible tablets that have been broken to adjust the dose of medicine can be stored at room temperature, between 68°F to 77°F (20°C to 25°C), and should be used within 7 days of having been broken. Tablet pieces may be returned to the opened blister and stored there out of reach of children for up to 7 days.	Adequate.
Active ingredient	bosentan	Revise to "bosentan monohydrate"
Inactive ingredients	Inactive ingredients in 32 mg dispersible tablets: cellulose microcrystalline, calcium hydrogen, phosphate anhydrous, croscarmellose sodium, silica colloidal anhydrous, tartaric acid, tutti frutti flavor, aspartame (E951), acesulfame potassium, and magnesium stearate.	• Replace "cellulose microcrystalline" with "microcrystalline cellulose." • Replace "calcium hydrogen phosphate anhydrous" with "dibasic calcium phosphate." • Replace "silica colloidal anhydrous" with "colloidal silicon dioxide." • List excipients in alphabetical order.

Reviewer's Overall Assessment: Adequate, pending the applicant's acceptance of the changes noted above.

QUALITY ASSESSMENT

Structured Product Labeling *- date of last update: 06Jun2017*

TRACLEER

bosentan tablet, soluble

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:66215-103
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
bosentan (UNII: Q326023R30) (bosentan anhydrous - UNII:XUL93R30K2)	bosentan anhydrous	32 mg

Inactive Ingredients

Ingredient Name	Strength
cellulose, microcrystalline (UNII: OP1R32D61U)	
anhydrous dibasic calcium phosphate (UNII: L11K75P92J)	
croscarmellose sodium (UNII: M28OL1HH48)	
silicon dioxide (UNII: ETJ7Z6XBU4)	
tartaric acid (UNII: W4888I119H)	
aspartame (UNII: Z0H242BBR1)	
acesulfame potassium (UNII: 23OV73Q5G9)	
magnesium stearate (UNII: 70097M6I30)	

Product Characteristics

Color	YELLOW (Pale yellow to off-white)	**Score**	4 pieces
Shape	CLOVER	**Size**	10mm
Flavor	TUTTI FRUTTI	**Imprint Code**	32
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:66215-103-56	4 in 1 CARTON	12/31/2017	
1		14 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA209279	11/20/2001	

QUALITY ASSESSMENT

Labeler – Actelion Pharmaceuticals US, Inc. (002641228)

Registrant – Actelion Pharmaceuticals, Ltd. (480007868)

Establishment

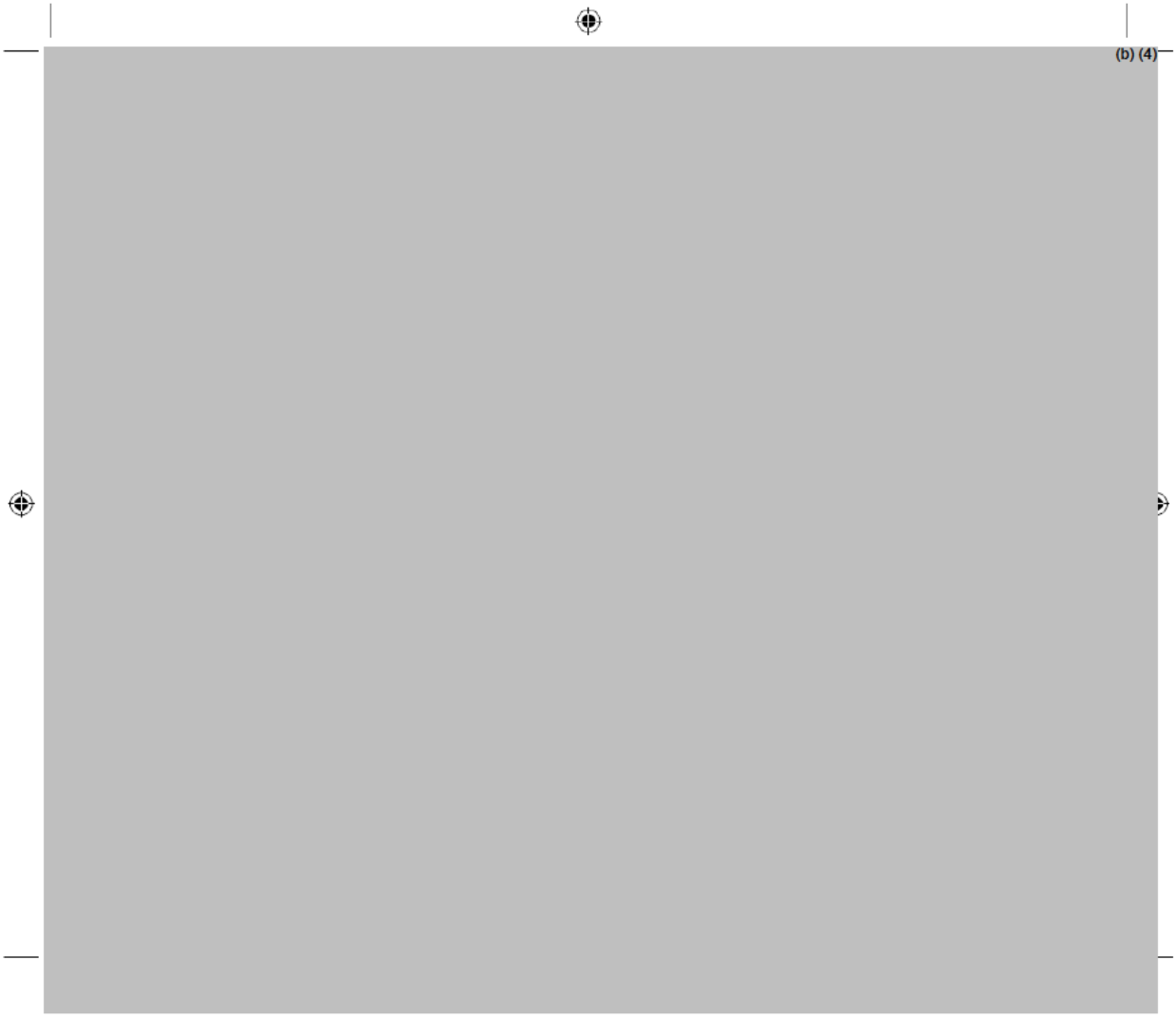
(b) (4)

[redacted]

Reviewer's Assessment: Inadequate. Revise product name from "tablet, soluble" to "tablet for oral suspension." Revise active ingredient from "bosentan anhydrous" to "bosentan monohydrate." Revise Business Operations for (b) (4) [redacted]

Labels

Immediate Container (Blister) Labels



Reviewer's Assessment: Adequate

Carton Labeling

(b) (4)

Reviewer's Assessment: Adequate.

List of Deficiencies:

Structured Product Labeling:

1. Revise product name from "tablet, soluble" to "tablet for oral suspension."
2. Revise active ingredient from "bosentan anhydrous" to "bosentan monohydrate."
3. Revise Business Operations for [redacted (b) (4)] ."
4. Remove [redacted (b) (4)] as an [redacted (b) (4)] (tablets for oral suspension).

Stephanie Emory

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BIOPHARMACEUTICS

Product Background:

NDA: 209279

Drug Product Name / Strength: Tracleer (bosentan) Tablets for Oral Suspension, 32 mg

Route of Administration: Oral

Applicant Name: Actelion Pharmaceuticals, Ltd.

Review Summary:

The Applicant's Tracleer® (bosentan) Tablets (62.5 and 125 mg) were approved for the treatment of pulmonary arterial hypetension (PAH) under NDA 021290. In the current 505(b)(1) application (NDA 209279), the Applicant is seeking approval for a 32 mg strength tablet for oral suspension as a treatment option for pediatric PAH patients.

The Applicant's initial proposal of using (b) (4) in lieu of dissolution testing was not accepted based on ICH Q6A guidelines. Based on the provided dissolution data provided in several IR responses, the following revised dissolution method and acceptance criterion are acceptable and agreed upon.

Dissolution Method and Acceptance Criterion	
Apparatus	USP II (Paddle)
Rotation Speed	75 RPM
Medium	1M HCl pH 1.1 with 0.5% SDS
Volume	900 mL
Acceptance Criterion	Q= (b) (4)% in 15 minutes

The proposed Tracleer® Tablets for suspension, 32 mg are scored tablets. The Applicant provided dissolution data on half tables obtained by both non-mechanically and mechanically splitting on Batch YBXV (Technical Batch, quadrisected) to support the functional score of the proposed tablets. In line with the revised dosing instructions[1], the Applicant's initially proposed quadrisected tablet (double scored) will be changed to a single scored tablet in a Postmarket Commitment (PMC).

From the Biopharmaceutics perspective, NDA 209279 for Tracleer Tablets for suspension, 32 mg is recommended for **APPROVAL**.

[1] DARRTS: REV-CLINPHARM-21 (Primary Review), final date 04/11/2017

List Submissions being reviewed (table):

Submissions Reviewed	Document Date
Original Submission	8/5/2016
IR Response	12/22/2016
IR Response	3/6/2017
IR Response with dissolution method development report	4/4/2017
IR Response: update dissolution method development report with drug product batch information	5/10/2017
IR Response: dissolution data on whole and half tablets	6/19/2017
IR Response: dissolution acceptance criterion acknowledgement	6/28/2017

Highlight Key Outstanding Issues from Last Cycle: N/A (This is the 1st review cycle)

Concise Description of Outstanding Issues Remaining: None

BCS Designation

Reviewer's Assessment: The Sponsor did not request an official BCS designation. Bosentan is likely a BCS II or IV drug (low solubility).

Solubility:

Bosentan is insoluble in water (1.0 mg/100 ml) and in aqueous buffer solutions of pH 1 to 5 (0.1 mg/100 ml at pH 1.1, and 4.0; 0.2 mg/100 ml at pH 5.0), the solubility increases to 43 mg/100 ml at pH 7.5. Bosentan is freely soluble in acetone, acetonitrile, chloroform and is soluble in ethanol. The apparent pKa value of bosentan is 5.46. The octanol/water partition coefficient of bosentan at pH 4.0 is 3.1 and at pH 7.4 is 1.3[2].

Table 1 Solubility Profiles of Bosentan[3]

Solvent	Solubility (mg/100 mL)	
0.1 N Hydrochloric acid (pH 1.2)	0.1	slightly soluble
Buffer pH 4.0	0.1	slightly soluble
Buffer pH 5.0	0.2	slightly soluble
Buffer pH 7.5	43	freely soluble
Buffer pH 8.0	53	freely soluble
Buffer pH 8.5	93	freely soluble
Water	1	sparingly soluble

In the Applicant's dissolution method development report in submission dated April 4, 2017, they provided the following solubility data of Bosentan at three pH using SDS after stirring at 100 rpm for 1 hour.

[2] DARRTS: NDA 21290 REV-CLINPHARM-01 (General Review), final date 07/18/2001 and COR-NDAACTION-02 (Approvable), final date 09/17/2001

[3] Provided in IR response dated 12/22/2016 (Appendix 1)

Table 2 Measured solubility of Bosentan API at three pH in a USP II dissolution bath (37°C, 900 mL, 100 rpm, 60 minutes)

pH / surfactant	no surfactant (n=2)	0.1% SDS (n=2)	0.5% SDS (n=2)
pH 1.1 (1 M HCl)	insoluble	0.10 mg/mL	0.11 mg/mL
pH 4.5 (0.5 M acetate buffer)	0.008 mg/mL	0.05 mg/mL	0.11 mg/mL
pH 6.8 (0.5 M phosphate buffer)	0.016 mg/mL	0.11 mg/mL	0.11 mg/mL
reference	17-02-013	17-02-066	17-03-004

Permeability: Not provided

Drug Substance

Bosentan monohydrate is the same drug substance as the active ingredient in Tracleer® (bosentan) Tablets, 62.5 and 125 mg.

Formulation:

The proposed tablet is formulated to be dispersed in water to form a suspension before administration. The Applicant originally proposed "dispersible tablet" as the name of the dosage form, however; upon FDA recommendation, the name of the dosage form was changed during the review cycle to "tablet for oral suspension". The composition of the proposed tablet is shown in table 2 below.

Table 3 Composition of Bosentan Dispersible 32 mg tablet

Ingredient	Actual mass/tablet
Bosentan	
- in form of bosentan monohydrate	33.045 mg
Cellulose microcrystalline	(b) (4)
Calcium hydrogen phosphate anhydrous	
Croscarmellose sodium	
Silica colloidal anhydrous	
Tartaric acid	
Tutti frutti	
Aspartame	
Acesulfame potassium	
Magnesium stearate	
Mass of the dispersible tablets	290.00 mg

The Applicant's initially proposed tablet was cross scored (quadrisected). In order to avoid patient confusion and unintended tablet division into quarter-tablet parts**Error! Bookmark not defined.**, the Applicant accepted the Agency's advice to change the cross-score to a single score in the Postmarket Commitment (PMC).

Dissolution Method

The Applicant's dissolution method for the proposed dispersible tablets is summarized as follows:

Parameters	Original Method in 2004	Revised	Method for Tracleer® Tablets[4]
USP Apparatus type	USP II (Paddle)		
Rotation (rpm)	100 RPM	75 RPM	50 RPM
Medium	6.8 Phosphate Buffer with 0.1% SLS	1M HCl pH 1.1 with 0.5% SDS	1 % SLS in water
Volume (mL)	900 mL		
Temperature	37±0.5 °C		

In the original submission, the Applicant proposes to use (b) (4) testing in lieu of dissolution testing for the proposed Tracleer® dispersible tablets. The Applicant was requested to submit data to support the proposed (b) (4) instead of dissolution testing per ICH Q6A guideline (see IR in Appendix 1). However, in IR response # 4 dated 12/22/2016, the Applicant stated that they are unable to provide the requested information before the PDUFA date[5]. Therefore, the dissolution method is expected to be fully developed and implemented as part of the drug product specifications.

The Applicant claims that the dissolution method used for Tracleer® (bosentan) 62.5 and 125 mg tablets in NDA 021290 is found not appropriate for the proposed dosage forms, i.e. tablets for suspension. The Applicant developed a revised dissolution method (b) (4)

(b) (4)

[4] DARRTS: NDA 21290 REV-CLINPHARM-01 (General Review), final date 11/1/2001 and 07/18/2001

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(b) (4)

(b) (4)

Per the proposed label, the proposed whole or half Tracleer® tablets for oral suspension should be dispersed in water before administration[6]. In general, dissolution testing would be performed on the suspension, if the dosage form is tablet for suspension. However; since the proposed name of the dosage form was originally "dispersible tablets", the dissolution test was performed on the tablets. Considering that dissolution of a suspension is faster than dissolution of a tablet and thus the dissolution test on a tablet is expected to be more discriminating, the dissolution development conducted on tablets only is acceptable.

The revised dissolution method (i.e. *US Apparatus II at 75 rpm using 900 mL 1 M HCl pH 1.1 with 0.5% SDS*) is found acceptable for the QC of the proposed drug product.

Dissolution Acceptance Criterion:

In the IR response dated June 19, 2017 (Appendix 4), the Applicant proposed a dissolution acceptance criterion of NLT (b) (4)% (Q) in (b) (4) minutes. Based on the provided dissolution data, the Agency recommended a revised dissolution acceptance criterion in the IR letter dated June 21, 2017. The Applicant accepted the recommendation and revised the acceptance criterion to Q= (b) (4)% in 15 minutes in the IR response dated June 28, 2017 (Appendix 5).

Tablet score:

The proposed Tracleer® tablets for oral suspension, 32 mg are scored tablets. The Applicant provided dissolution data on half tables obtained by both non-mechanically and mechanically splitting on a technical batch YBXV (quadrisected) (Appendix 4 and 5), which supports the functional score of the proposed tablets. In line with the revised dosing instruction, the

[6] The term 'tablet, dispersible' is no longer used for approved drug products, and it has been replaced by the term 'tablet, for suspension', C-DRG-00201

Applicant's initially proposed quadrisected tablet (double scored) will be changed to a single scored tablet in a PMC, for which no additional dissolution data is required.

Bridging of Formulations:
The to-be-market formulation is the same as the one used in the clinical trial AC-052-365, 373, 374, 377, and 378, except for the change in scoring that will occur in a PMC.

Biowaiver Request: N/A
A biowaiver is not requested nor required for this NDA.

R Regional Information
Comparability Protocols: None

Post-Approval Commitments:
In line with the revised dosing instruction, the Applicant has agreed with the Agency to remove the non-functional score as a Post-Marketing Commitment (PMC).

Lifecycle Management Considerations: None

List of Deficiencies: None
Recommendations:
From the Biopharmaceutics perspective, NDA 209279 for Tracleer Tablets for suspension, 32 mg is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date:

Zhuojun Zhao, Ph.D. 7/13/2017

Secondary Reviewer Name and Date:

I concur with Dr. Zhao's assessment and recommendation.
Elsbeth Chikhale, Ph.D. 7/18/2017

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Mohan Sapru

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