CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214522Orig1s000

SUMMARY REVIEW

DIVISION OF CARDIOLOGY AND NEPHROLOGY

Divisional Memorandum

NDA: 214522 (TADLIQ, tadalafil oral suspension)

Sponsor: CMP Development

Reviewer: N. Stockbridge, M.D., Ph.D.

The product is tadalafil oral suspension 20 mg/5 mL. The application received a Complete Response on 23 February 2021 for issues relating to two manufacturing sites, one for drug substance testing and one for drug product manufacturing. Other aspects of the application were acceptable. The resubmission of 21 December 2021 was reviewed by OPQ (Chandramouli, Carver, Sahu, Xue, Adams; 27 May 2022) with resolution of the issues.

The review team and I concur on approval.

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/s/

NORMAN L STOCKBRIDGE
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Cross-Discipline Team Leader Review

Date	February 20, 2021
From	Sudharshan Hariharan
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 214522
Type	505(b)(2)
Applicant	CMP Development LLC
Date of Submission	April 23, 2020
PDUFA Goal Date	February 23, 2021
Proprietary Name / Established (USAN) names	TADLIQ / Tadalafil
Dosage forms / Strengths	Oral Suspension / 4 mg/mL
Proposed Indication(s)	Treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability
Recommendation:	*'Complete Response'*

Material Reviewed/Consulted	
Integrated Quality Review (2/12/21)	Sithamalli Chandramouli, Su (Soung) Tran (Drug Substance), David Claffey, Theodore Carver (Drug Product), Vidya Pai, Kumar Janoria (Process and Facility), Parnali Chatterjee, Poonam Delvadia (Biopharmaceutics), Denise Miller, Bryan Riley (Microbiology), Theodore Carver (Application Technical Lead)
Pharmacology-Toxicology Review (1/13/2021)	Xi Yang, Jean Wu
Clinical Pharmacology Review (2/16/21)	Kunal Jhunjhunwala, Sudharshan Hariharan
Clinical Review	NA
Division of Pediatric and Maternal Health Review (10/19/20)	Wenjie Sun, Miriam Dinatale, Lynne Yao
Division of Medication Error Prevention and Analysis Reviews (8/11, 8/13, 9/25/2020)	Danielle Harris, Maximilian Straka, Hina Mehta
Office of Study Integrity and Surveillance Review (8/3/20)	Nicola Fenty-Stewart
Office of Prescription Drug Promotion Reviews (12/31/20, 1/4/21)	Jessica Chung, Zarna Patel

1. Introduction

On April 23, 2020, CMP Development LLC submitted a New Drug Application (NDA) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for TADLIQ (the final agreed upon tradename), an oral suspension of tadalafil, for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability.

The application relies on the Agency's previous finding of safety and effectiveness for the reference listed drug, ADCIRCA tablets (NDA 22332, approved 2009). No new clinical efficacy data are submitted in this application and no new claims are being sought with this application.

2. Background

Tadalafil is an inhibitor of phosphodiesterase type 5 (PDE5), the enzyme responsible for the degradation of cyclic guanosine monophosphate (cGMP). PAH is associated with impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations in the pulmonary vascular smooth muscle. PDE5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE5 by tadalafil increases the concentrations of cGMP resulting in relaxation of pulmonary vascular smooth muscle cells and vasodilation of the pulmonary vascular bed.

In adults, the recommended dose is 40 mg taken once-daily with or without food.

The applicant has developed a ready-to-use tadalafil oral suspension to replace the requirement of extemporaneous compounding of tablets into a suspension by either pharmacists or caregivers for treatment in patients who have difficulty swallowing tablets. The applicant proposes the same dose and dosing regimen for the oral suspension of tadalafil as approved for ADCIRCA for the proposed indication.

3. Product Quality

Office of Product Quality (OPQ) does not recommend approval of the application due to deficiencies identified in the drug product manufacturing and testing facilities.

Following is the summary of quality assessment from Integrated Quality Review by Dr. Carver:

Tadalafil oral suspension, a new formulation of tadalafil USP, is a white to off-white aqueous suspension to be marketed as a single strength of 20 mg/5mL (4 mg/mL). The drug product contains excipients that contribute to maintaining the quality of the drug product in suspension form during storage and use, including (b) (4) *mg/mL glycerin,* (b) (4) *mg/mL xanthan gum,* (b) (4) *mg/mL polysorbate 80, and* (b) (4) *simethicone emulsion. In addition, the product is* (b) (4) *citric acid monohydrate and trisodium citrate dihydrate,* (b) (4) *sodium benzoate* (b) (4) *peppermint flavor* (b) (4) *. The product is packaged in 150 mL* (b) (4) *bottles with a white plastic cap. No dosing device is co-packaged with the drug product. The manufacturing of the drug substance, the specifications, and supporting stability data for the drug product were found to be adequate. However, the drug product manufacturing and testing facilities,* (b) (4) *have unresolved facility deficiencies resulting in a Withhold*

status, requiring on-site inspections after resolution of these deficiencies. Additional non-approvability issues were also noted during review of the drug product manufacturing process.

OPQ clarified (email 22 February 2021) that responses to deficiencies in (b) (4) facility were reviewed during the current NDA review cycle and the responses remain inadequate.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were submitted as part of the application. All nonclinical findings with ADCIRCA can be borrowed based on an acceptable bridge to the listed drug. There are no novel excipients and there are no issues for impurities that require nonclinical safety evaluation.

5. Clinical Pharmacology

Office of Clinical Pharmacology (OCP) recommends approval of the oral suspension of tadalafil with or without food. The applicant conducted a randomized, three-way crossover study (Study No. 19-016) characterizing the pharmacokinetics of tadalafil following administration of the oral suspension and the listed drug, ADCIRCA, under fasted conditions. The study also assessed the effect of food for the oral suspension. The results show that both the peak concentration (C_{max}) and the area under the curve (AUC_{0-72}) for tadalafil is bioequivalent between the oral suspension and ADCIRCA, thus establishing a bridge to borrow Agency's previous finding of safety and effectiveness for ADCIRCA. A high-fat meal increased the rate (C_{max} 13%↑) and extent of absorption (AUC_{0-72} 19%↑) of tadalafil compared to fasted state. However, the modest change in exposure with food is within the pharmacokinetic variability of tadalafil that the effect of food is not clinically significant. The lack of no significant food effect for the oral suspension is consistent with the food effect results reported earlier for ADCIRCA.

Site Inspection:
OCP requested inspection of the clinical and bioanalytical sites at (b) (4) where the clinical study and bioanalysis of samples were conducted. OSIS recommends accepting the clinical data as the clinical and bioanalytical sites were inspected in the recent past with 'No Action Indicated' classification.

6. Clinical/Statistical- Efficacy

As discussed under Clinical Pharmacology, the relative bioavailability study provides the bridge to the efficacy findings of the listed drug, ADCIRCA.

7. Safety

This application primarily relies on the Agency's previous determination of safety for the listed drug, ADCIRCA.

8. Advisory Committee Meeting

The application does not raise significant issues regarding the safety or effectiveness of the drug; hence, no Advisory Committee Meeting was held or needed.

9. Pediatrics

This application triggers Pediatric Research Equity Act (PREA) because it is a new dosage form. The applicant requested a full waiver for the entire pediatric population because studies are impossible or highly impracticable; however, the agreed upon iPSP contained a plan for deferral of pediatric studies.

During the review period, discussions took place between DCN, DPMH and PeRC regarding the feasibility of conducting pediatric trials for the proposed indication. The consensus of these discussions was that pediatric studies are currently impracticable due to: (1) the lack of an acceptable bridging biomarker[1], (2) the inability to rely on a clinically meaningful outcome measure within the anticipated duration of a pediatric trial, and (3) reluctance on the part of clinicians and parents/caregivers to enroll pediatric patients in a placebo-controlled trial. While there are reasonable approaches to minimize placebo-controlled periods, the larger issues relate to clinical endpoints and lack of an acceptable bridging biomarker.

PeRC agreed that a full waiver of pediatric studies for impracticability is reasonable until one or more of the issues noted above is addressed.

10. Other Relevant Regulatory Issues

None.

11. Labeling

A final agreement on labeling was not reached with the applicant because of the planned 'Complete Response' action at the end of the review cycle. The proposed proprietary name, TADLIQ, is accepted by DMEPA.

12. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
Complete Response – Due to deficiencies identified in the drug product manufacturing and testing facilities.

Risk Benefit Assessment
For the indications sought, the risk-benefit of TADLIQ when used as directed in the proposed label is not expected to be different compared to ADCIRCA.

[1] Although pulmonary vascular resistance (PVR) as measured by right heart catheterization (RHC) was used as a bridging biomarker to support approval of Tracleer® (bosentan) for pediatric PAH, RHC is no longer considered ethical for the purposes of evaluating drug's effect in pediatric clinical trials due to its associated risk.

Recommendation for Postmarketing Risk Evaluation and Management Strategies
None

Recommendation for other Postmarketing Requirements (PMR) and Commitments
None

Recommended Comments to Applicant
Additional comments related to drug product manufacturing should be sent along with the Complete Response Letter.

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/s/

SUDHARSHAN HARIHARAN
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