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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA Number	214522
Submission Date	04/23/2020
Submission Type	505(b)(2)
Generic name	Tadalafil
Brand name	TADLIQ™
Applicant	CMP Development LLC
Dosage form	Oral suspension
Strength	20 mg/5 mL (4 mg/mL) supplied in 150 mL bottle
Drug Class	Phosphodiesterase 5 (PDE5) inhibitor
Indications	Treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability
Associated IND	(b) (4)
OCP Division	Division of Cardiovascular & Endocrine Pharmacology (DCEP)
OND Division	Division of Cardiology and Nephrology (DCN)
Primary Reviewer	Kunal Jhunjhunwala, MS, PhD
Secondary Reviewer	Sudharshan Hariharan, PhD

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1. EXECUTIVE SUMMARY

CMP Development LLC has submitted a 505(b)(2) NDA seeking approval for tadalafil oral suspension 4 mg/mL (TADLIQ™) relying on the Agency's findings of safety and effectiveness for the reference listed drug (RLD), ADCIRCA® tablets (NDA 22332). The applicant has developed an oral suspension that can be used as an alternative to tablets. TADLIQ is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. No additional clinical efficacy data is presented in this application and no new indication or claims are being requested with this application.

The applicant has conducted one clinical pharmacology study with two components: An open-label, balanced, randomized, single-dose, two-treatment, three-sequence, three-period, crossover in healthy adult human subjects to evaluate (1) bioequivalence between tadalafil 4 mg/mL oral suspension (5 mL equivalent to the dose of 20 mg tadalafil) and 20 mg ADCIRCA tablets under fasting condition, and (2) food effect study of tadalafil 4 mg/mL oral suspension (5 mL equivalent to the dose of 20 mg tadalafil).

1.1 Recommendations

The Office of Clinical Pharmacology/ Division of Cardiovascular & Endocrine Pharmacology (OCP/ DCEP) has reviewed the NDA submission. The results of the relative bioavailability (BA) and food effect assessments support approval of TADLIQ for the proposed indication at the doses as approved for the listed drug, ADCRICA. The food effect study results support administration of TADLIQ with or without food.

1.2 Post-Marketing Requirements and Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

- The results of the relative BA assessment demonstrate that TADLIQ is bioequivalent to ADCIRCA under fasted conditions. The results of the relative BA assessment are summarized in ***Table 3***.

- The results of food effect assessment show that fed state administration of tadalafil oral suspension increased the plasma exposure of tadalafil compared to the fasted state as measured by C_{max} (13%↑) and $AUC_{0\text{-}72h}$ (19%↑). These modest increase in exposures are not clinically significant. The results of the food effect assessment is summarized in **Table *4***.

- The bioanalytical method used to measure tadalafil is validated and the performance of the method in the clinical study is acceptable as per the specifications outlined in the Bioanalytical Method Validation Guidance (see **Table 2**).

2. QUESTION BASED REVIEW

This is an abridged version of the question-based review. For a detailed review of the clinical pharmacology attributes of tadalafil, refer to the original NDA 22332.

2.1 General Attributes of the Drug Product

Tadalafil oral suspension is white to off-white opaque suspension with a peppermint flavor. It will be manufactured and available as 20 mg/5 mL (4 mg/mL) strength supplied in a 150 mL bottle.

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Tadalafil oral suspension contain the following inactive ingredients: sodium benzoate, xanthan gum (b) (4) sucralose, glycerin, citric acid monohydrate, tri-sodium citrate dihydrate, polysorbate 80 (b) (4) 30% simethicone emulsion, (b) (4) peppermint flavor (b) (4).

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

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.

2.1.4 What are the proposed dose(s)?

The proposed doses are the same as those for ADCIRCA. The recommended dose of TADLIQ is 40 mg (10 mL) taken once daily with or without food.

2.2 Specific Review Questions

2.2.1 What are the design features of clinical pharmacology studies used to support dosing or label claims?

The applicant submitted one clinical pharmacology study (19-016) with two components (***Table 1***): (1) oral bioequivalence assessment comparing the bioavailability between tadalafil oral suspension (5 mL of 4 mg/mL) and 1 tablet of 20 mg ADCIRCA following single oral dose administration under fasted condition, (2) food effect assessment which evaluated the effect of high-fat meal on the bioavailability of single dose of tadalafil oral suspension.

Table 1. Summary of clinical pharmacology studies

Study	Type	Title	Study participants
19-016	Relative bioavailability and food effect study	An open-label, balanced, randomized, single-dose, two-treatment, three-sequence, three-period, crossover, oral bioequivalence study of tadalafil 4 mg/mL suspension (5 mL equivalent to the dose of 20 mg) with ADCIRCA (tadalafil) tablets 20 mg in healthy adult human subjects under fasting condition & food effect study of tadalafil 4 mg/mL suspension (5 mL equivalent to the dose of 20 mg) in healthy adult human subjects under fasting and fed conditions.	Randomized: 33 Completed: 32

2.2.2 Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

An LC-MS/MS method for the estimation of tadalafil in human plasma was developed and validated over a calibration range of 2 to 2068 ng/mL. Tadalafil-D3 was used as the internal standard (IS) for tadalafil. Sample preparation was done by liquid-liquid extraction technique. The chromatography was performed using an ACE, 50 x 4.6mm, 5µ column and analyzed by electrospray mass spectrometry in a positive ion mode. LC-MS/MS system consists of a Model-Shimadzu Pump-LC-10AD Column Oven- CTO-10 AS VP Autosampler-SIL-HTc HPLC and an API 3000 MS. Methanol: 2 mM Ammonium Acetate (70:30) (v/v) with a flow rate of 0.6 mL/min was used as mobile phase. Tadalafil eluted at approximately 1.9 minutes. The internal standard tadalafil d3 co-eluted with tadalafil. Calibration curve was found to be linear from 2 to 2068 ng/mL. Accuracy and precision of QC samples were within ±15% (and ±20% at LLOQ), and calibration curves for the LC-MS/MS bioanalytical assay were within acceptable limits. Greater than two-thirds (99.2%) of the incurred samples concentration results were within 20% of the original concentration of the respective samples, thus meeting the acceptance criteria for incurred samples reanalysis.

Analytical methods were validated and performed within acceptable limits as shown in **Table 2**.

Table 2. Summary of bioanalytical sample analysis and method validation

Analyte	Tadalafil
Method	LC-MS/MS
Internal Standard	Tadalafil -D3
Matrix	Human K_2EDTA Plasma

Extraction	Liquid-liquid Extraction
LLOQ (ng/mL)	2.002
CCs (ng/mL)	2.02, 4.05, 103.41, 413.66, 827.32, 1240.92, 1654.57, 2068.21
QCs (ng/mL)	LQC – 5.18 MQC – 820.78 HQC – 1630.7
Accuracy Intra-assay Accuracy (% Nominal) Inter- assay Accuracy (% Nominal)	 99.4 to 108.4 100 to 105.9
Precision Inter- assay Precision (%CV) Intra- assay precision (%CV)	 1.13 to 4.23 0.4 to 4.8
Recovery%	LQC- 89.81 MQC- 89.36 HQC- 90.62

CCs: Calibration Curve standards, QCs: Quality Control Samples, LLOQ: Lower Limit of Quantification
Source: Method validation and analytical reports (\\CDSESUB1\evsprod\nda214522\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\19-016\fasting-and-fed-study-1653-method-validation-report.pdf)

2.2.3 What is the relative bioavailability of tadalafil oral suspension (4 mg/mL) compared to ADCIRCA tablets? Does it support the proposed dosing?

The geometric mean ratios along with its 90% confidence interval (CI) of C_{max} and AUC_{0-t} for tadalafil oral suspension (4 mg/mL) compared to ADCIRCA are summarized in ***Table 3***. Because of the long half-life of tadalafil, AUC was truncated to 72 hours. The mean plasma concentration-time profile of tadalafil for the two treatments is shown in **Figure *1***.

Table 3. Results from relative bioavailability study

Relative Bioavailability Study		
Parameter	**Geometric mean ratio of Tadalafil oral suspension /ADCRICA (%)**	**90% CI**
C_{max}	95.5	89.8 – 101.4
AUC_{0-72h}	99.5	94.4 – 104.9

Source: Clinical Study Report of Study 19-016

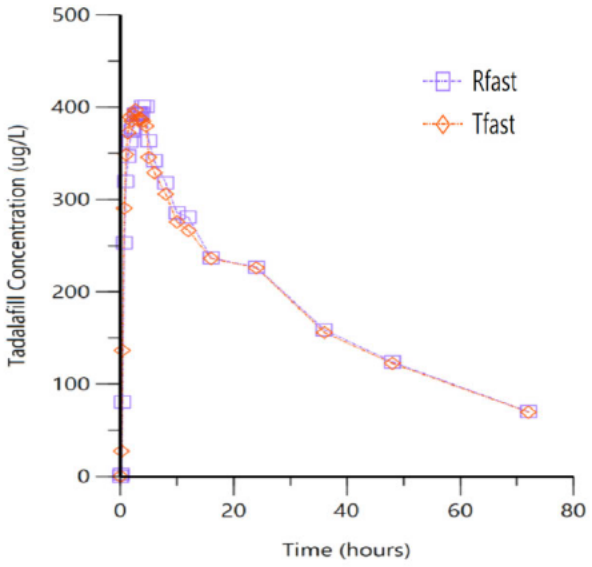

Figure 1. Mean plasma concentration-time profile of tadalafil for the oral suspension (T) versus ADCIRCA tablets (R)
Source: Reviewer's Analysis of data from Study 19-016

- The time taken to reach peak tadalafil plasma concentration for oral suspension compared to ADCIRCA tablets was unaffected, median Tmax of 2 h for both. This indicates that dissolution and absorption of tadalafil is unaffected when administered as an oral suspension compared to tablets.
- The pharmacokinetic variability of tadalafil following administration of tadalafil oral suspension was similar compared to ADCIRCA tablets - C_{max}: 19.2% (T) vs 19.5 (R); AUC_{0-72h}: 25.7% (T) vs 28.9% (R).
- Based on results shown in ***Table 3***, TADLIQ is bioequivalent to ADCIRCA. The dosing recommendations approved for ADCIRCA applies to TADLIQ.

2.2.4 What is the effect of food on the bioavailability of the drug from the drug product?

The geometric mean ratios along with its 90% CI for Cmax and AUC0-t following administration of tadalafil oral suspension with high-fat meal compared to fasted state administration is summarized in **Table *4***. The standardized breakfast (high-fat diet) increased the plasma exposure of the drug compared to the fasted state as measured by C_{max} (13%↑) and AUC_{0-72h} (19%↑). The modest magnitude of change in exposure with high-fat meal is within the pharmacokinetic variability of tadalafil such that the food effect for tadalafil oral suspension is not clinically significant. These results are consistent with the lack of food effect noted for the RLD, ADCIRCA tablets. TADLIQ can be taken with or without food.

Table 4. Geometric mean ratio (GMR) and 90% confidence interval for Fed/Fasted state administration of tadalafil oral suspension

Comparison of fed and fasted state administration

Parameter	Geometric mean ratio of fed/fasted state (%)	90% CI
C_{max}	112.5	101.7 – 124.4
$AUC_{0\text{-}72h}$	119.1	110.4 – 128.5

Source: Clinical Study Report of Study 19-016

3. APPENDICES

3.1 Relative bioavailability and food effect assessment study report

Study No: 19-016	**EDR:** \\CDSESUB1\evsprod\nda214522\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\19-016\study-report-body.pdf
Study Date: October 4th 2019 to December 5th 2019	
Title of Study: An open-label, balanced, randomized, single-dose, two-treatment, three-sequence, three-period, crossover, oral bioequivalence study of tadalafil 4 mg/mL suspension (Dose: 5 mL equivalent to the dose of 20 mg) (b) (4) with ADCIRCA tablets 20 mg (Reference: Eli Lilly and Company, Indianapolis, IN, USA) in healthy adult human subjects under fasting condition and food effect study of tadalafil 4 mg/mL suspension (Dose: 5 mL equivalent to the dose of 20 mg) (b) (4) in healthy adult human subjects under fasting and fed conditions.	
Investigational Products **Test (T):** Tadalafil 4mg/mL suspension (Dose: 5 mL equivalent to the dose of 20 mg) **Reference (R):** ADCIRCA tablets 20 mg	
Study: • **Design:** An open label, balanced, randomized single-dose, two-treatment, three-sequence, three-period, crossover, oral bioequivalence study in healthy adult human subjects under fasting condition and food effect study in healthy adult human subjects under fasting and fed conditions. • **Washout:** A washout period of 15 days (i.e., at least five elimination half-lives) was kept between each dose administration. • **Study participants:** A total of 33 healthy adult human subjects were dosed in the study and 32 of them completed the study. Subsequent dropouts/ withdrawals (after dosing) were not replaced. • **Fasted state:** All subjects were fasted (overnight) for at least 10 hours prior to dosing. Drinking water was not allowed from one hour before until one hour after dosing (except approximately 240 mL of water given during dosing) in each period. • **Fed state:** All subjects were required to fast (overnight) for at least 10 hours prior to the high-fat, high-calorie breakfast. • **Sampling times (h):** The pre-dose (-1.00 hour) blood samples of 4 mL was collected within one hour prior to dosing in each period. Subsequent samples of 4 mL each were collected at 0.17, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48- and 72-hours post-dose in each period. **Pharmacokinetic (PK) parameters calculated:** AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$, and K_{el} **Analytical Method:** • Plasma concentrations of tadalafil were determined by a validated LC-MS/MS method in the (b) (4)	

- Detailed analytical method is described in \\CDSESUB1\evsprod\nda214522\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\19-016\fasting-and-fed-study-165-analytical-study-report.pdf
- The analytical range for tadalafil in plasma was (b) (4) ng/mL

Reviewer comment: The performance of the analytical method is acceptable per the specifications in Bioanalytical Method Validation Guidance.

Statistical Methods:
The Ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-72h} were subjected to Analysis of Variance (ANOVA) for bioequivalence assessment. The model included sequence, subject (sequence), period and formulation effects as fixed effects factors.
For each pharmacokinetic parameter, the least squares mean was computed for each treatment and the difference between treatments, along with its 90% confidence interval, was exponentiated. The geometric mean ratio Test (fasted) versus Reference (fasted) and Test (fed) versus Test (fasted) and its confidence interval were used to summarize the relative bioavailability of tadalafil formulations and the effect of food, respectively.

Results:
32 subjects completed the study.

Table 1. Demographics

Age range	19 - 38 years
Males Females	100 % 0%
Weight	50.9 – 82.3 kg

Source: Clinical Study Report Study 19-016

Table 2. Statistical Summary of Relative BA Data (T_{fast} V R_{fast})

Parameter	Geometric Least Squares Mean (ln-transformed) (CV%)		T/R Ratio (%)	90% C. I.
	T	R		
C_{max} (ng/mL)	429.6 (19.2)	450 (19.5)	95.5	89.9 – 101.4
AUC_{0-72h} (ng.h/mL)	12499.6 (25.7)	12558.7 (28.9)	99.5	94.4 – 104.9

Source: Clinical Study Report Study 19-016

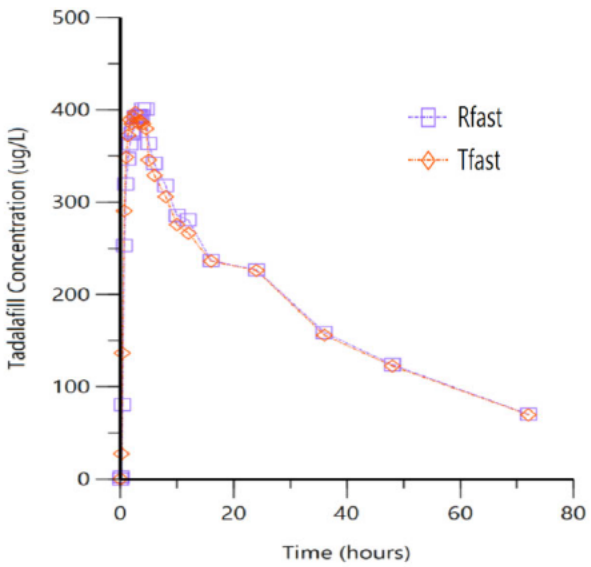

Table 3. Statistical Summary of Relative BA Data (T_{fast} V T_{fed})

Parameter	Geometric Least Squares Mean (ln-transformed) (CV%)		T/R Ratio (%)	90% C. I.
	Tfed	Tfast		
C_{max} (ng/mL)	479.6 (33.3)	426.4 (18.7)	112.5	101.7 – 124.4
AUC_{0-72h} (ng.h/mL)	14808.7 (35.2)	12435.1 (25.9)	119.1	110.4 – 128.5

Source: Clinical Study Report Study 19-016

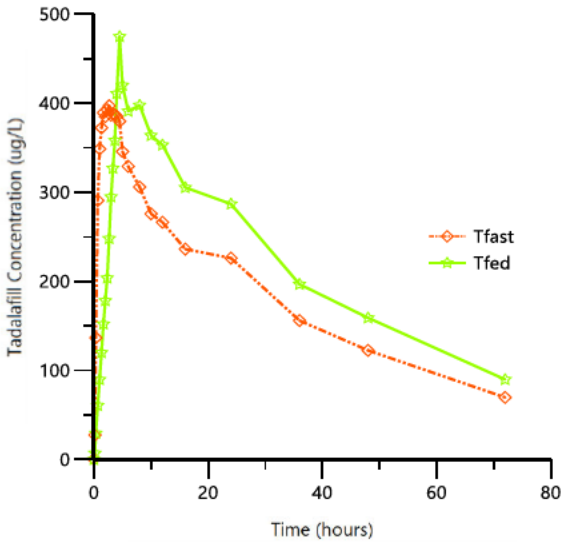

Figure 1: Linear Plot of mean (SE) Tadalafil concentration vs time profiles
Source: Reviewer's analysis

Conclusions:
The results of the relative BA study show that peak exposure (C_{max}) and total exposure (AUC_{0-72h}) for tadalafil oral suspension is bioequivalent to ADCIRCA tablets. The results from food effect study demonstrate that fed state administration of the tadalafil oral suspension increased the plasma exposure of tadalafil compared to the fasted state as measured by C_{max} (13%↑) and AUC_{0-72h} (19%↑).

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