CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214952Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 214952	Submission Date(s): 10/5/2020
Brand Name	Liqrev®
Generic Name	Sildenafil
Clinical Pharmacology Reviewer	Brianna Cote, PharmD, PhD
Clinical Pharmacology Team Leader	Manoj Khurana, PhD
OCP Division	DCEP
OND Division	DCN
Sponsor	CMP Development, LLC
Submission Type; Code	Original-1
Formulation; Strength(s)	Suspension; 10 mg/mL
Indication	Pulmonary arterial hypertension (PAH)

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1. Executive Summary

LIQREV® (sildenafil 10 mg/mL oral suspension) is a phosphodiesterase-5 (PDE-5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH). Sildenafil was initially approved by the agency in 1998. This package for Liqrev® was received by the Agency on October 5, 2020, and is submitted by the Applicant, CMC Development LLC, as a 505(b)(2) NDA.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) has reviewed NDA 214952 submitted on 10/5/2020 and finds it acceptable. This recommendation and labeling comments should be conveyed to the sponsor as appropriate.

1.2 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

This 505(b)(2) NDA relies on the results from the phase 1 pivotal clinical pharmacology study 19-014, an open-label, balanced, randomized, single-dose two-treatment, three-sequence, three-period, crossover, oral bioequivalence study of sildenafil 10 mg/mL oral suspension with Revatio 20 mg tablets in healthy, adult, human subjects under fasting condition, and food effect study of Sildenafil 10 mg/mL oral suspension in healthy, adult, human subjects under fasting and fed conditions. This study was completed in healthy adult Asian males in India aged 19 to 38 years.

The following are the key results from the clinical pharmacology study with regards to sildenafil and the metabolite, piperazine N-desmethyl sildenafil systemic exposure:

- Statistical comparison of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ data for the sildenafil 10 mg/mL oral suspension and the Revatio 20 mg tablets indicated that the two formulations are bioequivalent for sildenafil and the metabolite, piperazine N-desmethyl sildenafil, exposure.

- Administration under the fed condition did not affect AUC_{0-t} and $AUC_{0-\infty}$ of sildenafil and the metabolite, piperazine N-desmethyl sildenafil, for the sildenafil 10 mg/mL oral suspension compared to the fasted state.

- After administration of sildenafil 10 mg/mL oral suspension with food, the C_{max} of sildenafil and piperazine N-desmethyl sildenafil was decreased by 52.93% and 49.5% (excluding unreliable data; see Table 11 in Appendix), respectively.

- The statistical comparison of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ data after excluding certain subjects for which the data was flagged by OSIS inspection as unreliable for the sildenafil metabolite, piperazine N-desmethyl sildenafil, did not change the aforementioned conclusions on bioequivalence and food effect.

2. QBR

2.1 GENERAL ATTRIBUTES

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of sildenafil 10 mg/mL oral suspension?

The Applicant, CMP Development, LLC, submitted this 505(b)(2) application for sildenafil 10 mg/mL oral suspension.

The main objective of this 505(b)(2) NDA is to provide results from study 19-014 which assessed the bioequivalence, food effect, safety, and tolerability of sildenafil 10 mg/mL oral suspension.

The clinical pharmacology study 19-014 was an open-label, balanced, randomized, single-dose, two-treatment, three-sequence, three-period, crossover oral bioequivalence study of sildenafil 10 mg/ml oral suspension of (b) (4) (b) (4) comparing with Revatio 20 mg Tablets, Marketing Authorization holder: Pfizer Labs, Division of Pfizer Inc, NY, NY 10017 USA, in healthy, adult, human subjects under fasting condition and food effect study of the sildenafil 10 mg/ml oral suspension, in healthy, adult, human subjects under fasting and fed conditions.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What general clinical pharmacology features of sildenafil are relevant to the current submission?

For details on the clinical pharmacology of sildenafil, readers are referred to original NDA 021845 review for Revatio® (sildenafil citrate).

2.2.2 Is the sildenafil 10 mg/mL oral suspension formulation appropriately bridged to the Revatio® 20 mg tablet according to the pivotal clinical pharmacology study 19-014 data?

The data from the clinical pharmacology study 19-014 supports an adequate bridge between the sildenafil 10 mg/mL oral suspension formulation and the Revatio® 20 mg tablet through demonstration of bioequivalence for the pre-specified primary PK parameters – C_{max}, AUC_{0-t}, and AUC_{0-inf}. The study design and conduct (as reported) further supported these results.

The clinical pharmacology study 19-014 was an open-label, balanced, randomized, single-dose two-treatment, three-sequence, three-period, crossover, oral bioequivalence study of sildenafil 10 mg/mL oral suspension with Revatio 20 mg tablets in healthy, adult, human subjects under fasting condition, and food effect study of sildenafil 10 mg/mL oral suspension in healthy, adult, human subjects under fasting and fed conditions.

Those included in the study were Asian males aged 19 to 38 years. For each treatment, subjects were fasted overnight for at least 10 hours. When given the 20 mg Revatio® tablet, subjects swallowed with 240 mL of water. The suspension was to be swallowed with about 50 mL of water, the container was rinsed, then additional water was consumed such that the participant consumed 240 mL water total. For the food effect study, a high fat, high calorie breakfast was served 30 minutes before taking the suspension.

The objectives were to compare the rate and extent of absorption of sildenafil from the suspension and the Revatio tablets, evaluate the food effect of sildenafil oral suspension, and monitor the safety and tolerability of a single dose of suspension in healthy, adult, human subjects under fasting and fed conditions. Blood samples were taken up to 24 hours post-dose, and there was a washout period of 7 days between each period.

Analysis was conducted for both sildenafil and the metabolite, piperazine N-desmethyl sildenafil. In some tests, outliers were detected with a studentized residual (RStudent) test. The Applicant's findings including all subjects are summarized below in Tables 1 and 2, and tables in Appendix 4.1 show analysis results excluding outliers. Both inclusion and exclusion of outliers resulted in bioequivalence between the test and reference products with regards to primary PK parameters for sildenafil and the metabolite, piperazine N-desmethyl sildenafil.

The Applicant analysis showed that 2 mL of the sildenafil 10 mg/mL suspension was bioequivalent with the Revatio® 20 mg tablet under fasting conditions, with the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ 90% CI falling within the acceptable range for bioequivalence (80-125%).

Table 1. Sponsor Summary of Pharmacokinetic and Statistical Evaluation for Sildenafil (T_{fast} Vs R_{fast}) Examining Geometric Least Squares Means, Ratios and 90% Confidence Intervals for Pharmacokinetic Parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) of Sildenafil (N = 29) (Including Outlier)

Pharmacokinetic Parameters (Units)	Ln- transformed			90% Confidence Interval (Parametric)	
	Geometric Least Squares Mean				
	Test Product (T_{fast})	Reference Product (R_{fast})	T_{fast}/R_{fast} (%)	Lower	Upper
C_{max} (ng/mL)	221.7955	204.9694	108.21	99.88	117.24
AUC_{0-t} (ng.hr/mL)	571.8581	571.6905	100.03	93.97	106.48
$AUC_{0-\infty}$ (ng.hr/mL)	582.8809	582.2400	100.11	93.88	106.75

Source: Applicant, Study Synopsis, Table B

Table 2. Sponsor Summary of Pharmacokinetic and Statistical Evaluation for Piperazine N-Desmethyl Sildenafil (T_{fast} Vs R_{fast}) Examining Geometric Least Squares Means, Ratios and 90% Confidence Intervals for Pharmacokinetic Parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) of Sildenafil (N = 29) (Including Outliers)

Pharmacokinetic Parameters (Units)	Ln- transformed			90% Confidence Interval (Parametric)	
	Geometric Least Squares Mean				
	Test Product(T_{fast})	Reference Product (R_{fast})	T_{fast}/R_{fast} (%)	Lower	Upper
C_{max} (ng/mL)	35.7889	34.5417	103.61	93.44	114.89
AUC_{0-t} (ng.hr/mL)	154.2945	154.7123	99.73	93.63	106.22
$AUC_{0-\infty}$ (ng.hr/mL)	164.5251	164.3695	100.09	94.36	106.18

Source: Applicant, Study Synopsis, Table H

These findings for both sildenafil and the metabolite were reanalyzed and confirmed by the clinical pharmacology reviewer including all subjects who completed the study (see Appendix 4.1 Tables 9 and 10). Additionally, OSIS inspection review found that some data for subjects 8, 12, 18, and 21 for piperazine N-desmethyl sildenafil may not be reliable. Data was analyzed excluding these participants during certain periods (see note about OSIS findings in Section 2.3 and Table 11 in Appendix 4.1). This reanalysis confirmed the bioequivalence between the test and reference products under fasting conditions for piperazine N-desmethyl sildenafil, and thus did not affect the conclusions from the original analysis.

2.2.3 Does food affect the pharmacokinetics of sildenafil from the sildenafil 10 mg/mL oral suspension formulation?

The food effect evaluation part of the 19-014 study showed that in comparison to the administration of the sildenafil 10 mg/mL suspension under fasted state, the extent of absorption, as assessed from AUC_{0-t} and AUC_{0-inf}, was not affected. However, the C_{max} was decreased by 53% when the sildenafil 10 mg/mL suspension was administered under the fed state.

The Applicant analysis showed that for the sildenafil 10 mg/mL suspension, the AUC_{0-t} and $AUC_{0-\infty}$ geometric mean ratios and 90% CI values fell within 80-125%; however, the C_{max} was decreased by 53%. The Applicant's data including outliers is in Tables 3 and 4 below. Data excluding outliers is included in Appendix 4.1.

Findings for both sildenafil and the metabolite were reanalyzed and confirmed by the clinical pharmacology reviewer including all subjects who completed the study (See Appendix 4.1 Tables 9 and 10). Additionally, OSIS inspection review found that some data for subjects 8, 12, 18, and 21 for piperazine N-desmethyl sildenafil may not be

reliable. Data was analyzed excluding these participants during certain periods (see note about OSIS findings in Section 2.3 and Table 11 in Appendix 4.1). The AUC_{0-t} and $AUC_{0-\infty}$ geometric mean ratios and 90% CI values remained within 80-125%, and C_{max} still fell outside the 80-125% range and thus, the conclusions from the original analysis were not affected.

Table 3. Sponsor Summary of Pharmacokinetic and Statistical Evaluation for Sildenafil (T_{fed} Vs T_{fast}) Examining Geometric Least Squares Means, Ratios and 90% Confidence Intervals for Pharmacokinetic Parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) of Sildenafil (N = 29) (Including Outliers)

Pharmacokinetic Parameters (Units)	Ln- transformed Geometric Least Squares Mean			90% Confidence Interval (Parametric)	
	Test Product (T_{fed})	Test Product (T_{fast})	T_{fed}/T_{fast} (%)	Lower	Upper
C_{max} (ng/mL)	116.9859	221.7955	52.74	47.39	58.70
AUC_{0-t} (ng.hr/mL)	634.5058	571.8581	110.96	103.02	119.50
$AUC_{0-\infty}$ (ng.hr/mL)	651.1591	582.8809	111.71	103.75	120.29

Source: Applicant, Study Synopsis, Table E

Table 4. Sponsor Summary of Pharmacokinetic and Statistical Evaluation for Piperazine N-Desmethyl Sildenafil (T_{fed} Vs T_{fast}) Examining Geometric Least Squares Means, Ratios and 90% Confidence Intervals for Pharmacokinetic Parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) of Sildenafil (N = 29) (Including Outlier)

Pharmacokinetic Parameters (Units)	Ln- transformed Geometric Least Squares Mean			90% Confidence Interval (Parametric)	
	Test Product(T_{fed})	Test Product (T_{fast})	T_{fed}/T_{fast} (%)	Lower	Upper
C_{max} (ng/mL)	16.7483	35.7889	46.80	41.50	52.78
AUC_{0-t} (ng.hr/mL)	139.0099	154.2945	90.09	84.12	96.49
$AUC_{0-\infty}$ (ng.hr/mL)	150.9493	164.5251	91.75	85.93	97.97

Source: Applicant, Study Synopsis, Table K

The food effect study shows that although total exposure, as measured by AUC, is not affected by food, the C_{max} is lowered by 53%. Given the total exposure remain unchanged, the change in C_{max} is not clinically relevant and Liqrev can be administered with or without food.

2.3 Analytical Section

1. Summary of overall performance of the bioanalytical method:

- An LC-MS/MS method was developed for detection of sildenafil and N-desmethyl sildenafil in human plasma. The original method (method validation 1 – method validation ID MV-189-01) underwent full validation and was used 18th Apr, 2019, to 28th Apr, 2019. Several addendums were added after this initial method. Each addendum underwent a partial validation. One addendum was added, and this second method (method validation 2 – method validation ID MV-189-01 ADD 01) was used on 13th May, 2019. An additional addendum (method validation 3 – method validation ID MV-189-01 ADD 02) was added and used on 14th Jun, 2019, to 15th Jun, 2019. A third addendum (method validation 4 – method validation ID MV-189-01 ADD 03) was used on 21st Nov, 2019, to 22nd Nov, 2019, in Method SOP ID "MS-238-02". The clinical study took place 4th Oct, 2019, to 11th Nov, 2019, and used Method SOP ID "MS-238-02".

- The objective of the work in addendum 01 and 02 was to assess the long term stability of sildenafil and the metabolite in human plasma at -80 °C (operational temperature below -60.0 °C) and at -20.0 °C (operational temperature below -10.0 °C. The objective of the work in addendum 03 was to assess the long term stability of sildenafil and the metabolite in human plasma at -80.0°C (operational temperature below -60.0 °C).

- The matrix for the method validation of the original method, addendums, and the clinical study was from normal, healthy subjects.

- Method validation 4 had a calibration range of LLOQ-ULOQ 0.502-999.182 ng/mL for sildenafil, and LLOQ-ULOQ 0.512-647.597 ng/mL for N-desmethyl sildenafil.

- The clinical study had a calibration range of LLOQ-ULOQ 0.502-999.219 ng/mL for sildenafil, and LLOQ-ULOQ 0.512-646.046 ng/mL for N-desmethyl sildenafil.

- Sildenafil D8 and N-desmethyl sildenafil D8 were used as internal standards.

- For sildenafil, the QC nominal concentrations included 0.504 ng/mL (LLOQ), 1.373 ng/mL (LQC), 50.3 ng/mL (LMQC), 419.163 ng/mL (MQC), and 793.870 ng/mL (HQC). For method validation, the calibration curve performance during accuracy and precision runs was assessed. The calibration encompassed 10 standards ranging in concentration from 0.501 ng/mL to 1001.319 ng/mL. The precision and accuracy for standard 1 (0.501 ng/mL) was 0.68% and 101.60%, respectively. The precision and accuracy for standards 2-10 ranged from 0.83% to 3.42% and 92.16% to 103.23%, respectively. The QC intraday precision range for LQC, LMQC, MQC, and HQC was between

1.48% and 8.73%, and the precision for the LLOQ QC was 7.91%. The QC intraday accuracy range for LQC, LMQC, MQC, and HQC was between 88.57% to 101.09%, and the accuracy for the LLOQ QC was 95.27%. The QC interday precision range for LQC, LMQC, MQC, and HQC was between 2.26% and 7.96%, and the precision for the LLOQ QC was 7.25%. The QC interday accuracy range for LQC, LMQC, MQC, and HQC was between 92.37% and 102.65%, and the accuracy for the LLOQ QC was 99.75%. Hemolysis effect, lipemic effect, and dilution linearity and hook effect did not result in major changes to the accuracy and precision of the method.

- Benchtop, freeze-thaw, and long-term storage stability (in human plasma for up to 213 days at -80 °C) were assessed for sildenafil and were in the acceptable range.

- For N-desmethyl sildenafil, the QC nominal concentrations included 0.512 ng/mL (LLOQ), 1.403 ng/mL (LQC), 32.639 ng/mL (LMQC), 267.533 ng/mL (MQC), and 519.481 ng/mL (HQC). For method validation, the calibration curve performance during accuracy and precision runs was assessed. The calibration encompassed 10 standards ranging in concentration from 0.511 ng/mL to 650.621 ng/mL. The precision and accuracy for standard 1 (0.511 ng/mL) was 1.60% and 98.56%, respectively. The precision and accuracy for standards 2-10 ranged from 0.37% to 3.75% and 99.17% to 101.63%, respectively. The QC intraday precision range for LQC, LMQC, MQC, and HQC was between 2.01% and 12.31%, and the precision for the LLOQ QC was 11.65%. The QC intraday accuracy range for LQC, LMQC, MQC, and HQC was between 97.94% to 108.24%, and the accuracy for the LLOQ QC was 113.35%. The QC interday precision range for LQC, LMQC, MQC, and HQC was between 2.67% and 9.92%, and the precision for the LLOQ QC was 13.59%. The QC interday accuracy range for LQC, LMQC, MQC, and HQC was between 100.37% and 105.48%, and the accuracy for the LLOQ QC was 110.33%. Hemolysis effect, lipemic effect, and dilution linearity and hook effect did not result in major changes to the accuracy and precision of the method.

- Benchtop, freeze-thaw, and long-term storage stability (in human plasma for up to 213 days at -80 °C) were assessed for N-desmethyl sildenafil and were within the acceptable range.

- Method performance information for sildenafil during the analysis of clinical study samples is included below:

    - Standard curve performance in the study was assessed. The precision for standard 1 (LLOQ) was 1.63%, and the accuracy was 101.98%. For standards 2-10, the precision was 1.17% to 3.58%, and the accuracy was 96.18% to 104.16%.

    - The precision, accuracy, and nominal concentration of low, lower middle, middle, and high quality control samples during the study were

5.00% and 101.57% (LQC: 1.299 ng/mL), 2.69% and 102.6% (LMQC: 41.890 ng/mL), 2.47% and 102.08% (MQC: 418.905 ng/mL), and 2.34% and 102.43% (HQC: 794.132 ng/mL), respectively.

- A total of 210 samples were analyzed for sildenafil in three independent batches (72 samples of ISR 01, 66 samples of ISR 02, and 72 samples of ISR 03 batch). 206 of the 210 samples met the acceptance criteria (98.10%).

- The study sample storage period from first sample collection until the completion of analysis was 59 days at -80.0 °C (operational temperature: below -60 °C). Long term matrix stability duration was 213 days under these same conditions.

- Method performance information for N-desmethyl sildenafil during the analysis of clinical study samples is included below:

  - Standard curve performance in the study was assessed. The precision for standard 1 (LLOQ) was 2.35%, and the accuracy was 101.71%. For standards 2-10, the precision was 2.52 % to 5.05%, and the accuracy was 96.13% to 101.82%.

  - The precision, accuracy, and nominal concentration of low, lower middle, middle, and high quality control samples during the study were 7.89% and 103.13% (LQC: 1.317 ng/mL), 3.78% and 103.28% (LMQC: 10.129 ng/mL), 3.31% and 105.03% (MQC: 266.549 ng/mL), and 3.84% and 105.45% (HQC: 516.567 ng/mL), respectively.

  - A total of 210 samples were analyzed for N-desmethyl sildenafil in three independent batches (72 samples of ISR 04, 66 samples of ISR 05, and 72 samples of ISR 06 batch). 206 of the 210 samples met the acceptance criteria (98.10%).

  - The study sample storage period from first sample collection until the completion of analysis was 59 days at -80.0 °C (operational temperature: below -60 °C). Long term matrix stability duration was 213 days under these same conditions.

The bioanalytical method, as reported, seems to support the results and conclusions from the clinical pharmacology study 19-014; however, there were some concerns identified during the OSIS inspection that resulted in additional data analysis to confirm the Applicant's findings. N-desmethyl sildenafil data from subject (b) (6) during the fasting periods (periods 2 and 3 for both the reference and test products), subject (b) (6) during the fasting periods (periods 1 and 2 for both the reference and test products), subject (b) (6) during the fasting period for the test product (period 3), and subject (b) (6) during the fasting period for the reference product (period 3) were found to be unreliable. OSIS concluded that the "objectionable conditions were isolated in nature," and recommended excluding objectionable samples from the assessment of N-

desmethyl sildenafil. Bioequivalence data was re-analyzed excluding all N-desmethyl sildenafil data from the aforementioned subjects in the periods where data was found to be unreliable. Results of this analysis can be found in Appendix 4.1, Table 11. Though there were some differences in the calculations, the conclusions with and without these data points are the same.

3. Labeling Recommendations

Recommendations (Preliminary):

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology has the following labeling recommendations for revisions to the Applicant's proposed language based on the information reviewed under the current submission.

[Note: The blue text is the recommended revision and strikethrough text is the deletion]

Section/Proposed Language	Recommendation/ Comment
12. CLINICAL PHARMACOLOGY 12.2 Pharmacodynamics **Effects of LIQREV on Blood Pressure** Single oral doses of sildenafil 100 mg administered to healthy volunteers produced decreases in supine blood pressure (mean maximum decrease in systolic/diastolic blood pressure of 8/5 mmHg). The decrease in blood pressure was most notable approximately 1-2 hours after dosing, and was not different from placebo at 8 hours. Similar effects on blood pressure were noted with 25 mg, 50 mg and 100 mg doses of sildenafil, therefore the effects are not related to dose or plasma levels within this dosage range. Larger effects were recorded among patients receiving concomitant nitrates *[see Contraindications (4)]*. After chronic dosing of 80 mg three times a day sildenafil to healthy volunteers, the largest mean change from baseline in supine systolic and supine diastolic blood pressures was a decrease of 9.0 mmHg and 8.4 mmHg, respectively. After chronic dosing of 80 mg three times a day sildenafil to patients with systemic hypertension, the mean change from baseline in systolic and diastolic blood pressures was a decrease of 9.4 mmHg and 9.1 mmHg, respectively. After chronic dosing of 80 mg three times a day sildenafil to patients with PAH, lesser reductions than above in systolic and diastolic blood pressures were observed (a decrease in both of 2 mmHg). (b) (4) Single oral doses of sildenafil up to 100 mg in healthy volunteers produced no clinically relevant effects on ECG. After chronic dosing of 80 mg three times a day to patients with PAH, no clinically relevant effects on ECG were reported. (b) (4)	Text moved/ Reasonable

(b) (4)	
Add the following to Section 12.2. Pharmacodynamics: **Alcohol** Sildenafil (50 mg) did not potentiate the hypotensive effect of alcohol in healthy volunteers with mean maximum blood alcohol levels of 0.08%. .	Moved PD DDI potential language from 12.3
12.3 Pharmacokinetics Absorption (b) (4) (b) (4) Sildenafil is rapidly absorbed after oral administration, with a mean absolute bioavailability of 41% (25-63%). Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. (b) (4) In patients with PAH, the average steady-state concentrations were 20-50% higher when compared to those of healthy volunteers. There was also a doubling of C_{min} levels compared to healthy volunteers. Both findings suggest a lower clearance and/or a higher oral bioavailability of sildenafil in patients with PAH compared to healthy volunteers. (b) (4) (b) (4) When LIQREV is taken with a high-fat meal, the rate of absorption is reduced, with a mean delay in t_{max} of about 60 minutes and a mean reduction in peak plasma concentration (C_{max}) of 53%, while the extent of absorption (AUC) is increased by 11%. **Distribution** The mean steady state volume of distribution (Vss) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil and its major	Text moved/information added

circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.

(b) (4)

(b) (4) Both sildenafil and the active metabolite have terminal half-lives of about 4 hours.

Metabolism

Sildenafil is cleared predominantly by the CYP3A (major route) and cytochrome P450 2C9 (CYP2C9, minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-desmethylation of sildenafil, and is, itself, further metabolized. This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an in vitro potency for PDE-5 approximately 50% of the parent drug. In healthy volunteers, plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil, so that the metabolite accounts for about 20% of sildenafil's pharmacologic effects. In patients with PAH, however, the ratio of the metabolite to sildenafil is higher. ~~Both sildenafil and the active metabolite have terminal half-lives of about 4 hours.~~

Excretion

After (b) (4) oral (b) (4) administration, sildenafil is excreted as metabolites predominantly in the feces (approximately 80% of the administered oral dose) and to a lesser extent in the urine (approximately 13% of the administered oral dose).

~~**Population Pharmacokinetic**~~ (b) (4)

~~Age, gender, race, and renal and hepatic function were included as factors assessed in the population pharmacokinetic model to evaluate sildenafil pharmacokinetics in patients with PAH. The dataset available for the population pharmacokinetic evaluation contained a wide range of demographic data and laboratory parameters associated with hepatic and renal function. None of these factors had a significant impact on sildenafil pharmacokinetics in patients with PAH.~~

~~In patients with PAH, the average steady-state concentrations were 20-50% higher when compared to those of healthy volunteers. There was also a doubling of C_{min} levels compared to healthy volunteers. Both findings suggest a lower clearance and/or a higher oral bioavailability of sildenafil in patients with PAH compared to healthy volunteers.~~

(b) (4)

4. Appendix

4.1 ADDITIONAL ANALYSES/REVIEWERS ANALYSIS

SPONSOR'S ANALYSIS EXCLUDING OUTLIER:

Table 5. Sponsor Summary of Pharmacokinetic and Statistical Evaluation for Sildenafil (T_{fast} Vs R_{fast}) Examining Geometric Least Squares Means, Ratios and 90% Confidence Intervals for Pharmacokinetic Parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) of Sildenafil (N = 28) (Excluding Outlier)

Pharmacokinetic Parameters (Units)	Ln- transformed			90% Confidence Interval (Parametric)	
	Geometric Least Squares Mean				
	Test Product (T_{fast})	Reference Product (R_{fast})	T_{fast}/R_{fast} (%)	Lower	Upper
C_{max} (ng/mL)	213.7843	199.2043	107.32	98.88	116.48
AUC_{0-t} (ng.hr/mL)	537.1188	548.3469	97.95	92.96	103.21
$AUC_{0-\infty}$ (ng.hr/mL)	545.8285	557.8405	97.85	92.90	103.05

Source: Applicant, Study Synopsis, Table D

Table 6. Sponsor Summary of Pharmacokinetic and Statistical Evaluation for Piperazine N-Desmethyl Sildenafil (T_{fast} Vs R_{fast}) Examining Geometric Least Squares Means, Ratios and 90% Confidence Intervals for Pharmacokinetic Parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) of Sildenafil (N = 27) (Excluding Outliers)

Pharmacokinetic Parameters (Units)	Ln- transformed			90% Confidence Interval (Parametric)	
	Geometric Least Squares Mean				
	Test Product(T_{fast})	Reference Product (R_{fast})	T_{fast}/R_{fast} (%)	Lower	Upper
C_{max} (ng/mL)	36.3935	34.1903	106.44	97.56	116.14
AUC_{0-t} (ng.hr/mL)	154.6916	154.2822	100.27	95.56	105.20
$AUC_{0-\infty}$ (ng.hr/mL)	164.8983	164.0522	100.52	95.87	105.38

Source: Applicant, Study Synopsis, Table I

Table 7. Sponsor Summary of Pharmacokinetic and Statistical Evaluation for Sildenafil (T_{fed} Vs T_{fast}) Examining Geometric Least Squares Means, Ratios and 90% Confidence Intervals for Pharmacokinetic Parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) of Sildenafil (N = 27) (Excluding Outliers)

Pharmacokinetic Parameters (Units)	Ln- transformed			90% Confidence Interval (Parametric)	
	Geometric Least Squares Mean				
	Test Product (T_{fed})	Test Product (T_{fast})	T_{fed}/T_{fast} (%)	Lower	Upper
C_{max} (ng/mL)	118.5175	231.5109	51.19	45.89	57.11
AUC_{0-t} (ng.hr/mL)	645.4251	604.6276	106.75	100.20	113.73
$AUC_{0-\infty}$ (ng.hr/mL)	663.4435	616.8721	107.55	100.91	114.62

Source: Applicant, Study Synopsis, Table F

Table 8. Sponsor Summary of Pharmacokinetic and Statistical Evaluation for Piperazine N-Desmethyl Sildenafil (T_{fed} Vs T_{fast}) Examining Geometric Least Squares Means, Ratios and 90% Confidence Intervals for Pharmacokinetic Parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) of Sildenafil (N = 28) (Excluding Outlier)

Pharmacokinetic Parameters (Units)	Ln- transformed			90% Confidence Interval (Parametric)	
	Geometric Least Squares Mean				
	Test Product(T_{fed})	Test Product (T_{fast})	T_{fed}/T_{fast} (%)	Lower	Upper
C_{max} (ng/mL)	16.9888	37.7127	45.05	40.62	49.96
AUC_{0-t} (ng.hr/mL)	137.5760	155.6238	88.40	83.07	94.08
$AUC_{0-\infty}$ (ng.hr/mL)	148.0021	164.2375	90.11	84.90	95.65

Source: Applicant, Study Synopsis, Table L

REVIEWER'S REANALYSIS

Table 9. Reviewer Summary of Bioequivalence Analyses for Sildenafil

Reviewer's Calculations – Cmax (ng/mL) (Fasting)				
Tfast	**Rfast**	**Ratio (%)**	**90% Lower (%)**	**90% Upper (%)**
221.3	205.3	107.8	98.0	118.6
Reviewer's Calculations – Cmax (ng/mL) (Food Effect)				
Tfast	**Tfed**	**Ratio (%)**	**90% Lower (%)**	**90% Upper (%)**
221.3	117.1	52.9	48.1	58.2
Reviewer's Calculations – AUC(0-t) (ng.hr/mL) (Fasting)				
Tfast	**Rfast**	**Ratio (%)**	**90% Lower (%)**	**90% Upper (%)**
570.5	572.3	99.7	92.4	107.5
Reviewer's Calculations – AUC(0-t) (ng.hr/mL) (Food Effect)				
Tfast	**Tfed**	**Ratio (%)**	**90% Lower (%)**	**90% Upper (%)**
570.5	635.3	111.4	103.2	120.1
Reviewer's Calculations – AUC(0-inf) (ng.hr/mL) (Fasting)				
Tfast	**Rfast**	**Ratio (%)**	**90% Lower (%)**	**90% Upper (%)**
581.5	582.8	99.8	92.4	107.7
Reviewer's Calculations – AUC(0-inf) (ng.hr/mL) (Food Effect)				
Tfast	**Tfed**	**Ratio (%)**	**90% Lower (%)**	**90% Upper (%)**
581.5	652.1	112.1	103.9	121.1

Source: Clinical Pharmacology Reviewer's Analysis
Values for T_{fast}, R_{fast}, and T_{fed} are Geometric Least Squares Means
Applicant-provided data from SAS files were analyzed for bioequivalence using Phoenix 64 Software by Certara.

Table 10. Reviewer Summary of Bioequivalence Analyses for Piperazine N-Desmethyl Sildenafil

Reviewer's Calculations – Cmax (ng/mL) (Fasting)				
Tfast	**Rfast**	**Ratio (%)**	**90% Lower (%)**	**90% Upper (%)**
35.7	34.6	103.4	92.9	115.1
Reviewer's Calculations – Cmax (ng/mL) (Food Effect)				
Tfast	**Tfed**	**Ratio (%)**	**90% Lower (%)**	**90% Upper (%)**
35.7	16.8	46.9	42.2	52.2
Reviewer's Calculations – AUC(0-t) (ng.hr/mL) (Fasting)				
Tfast	**Rfast**	**Ratio (%)**	**90% Lower (%)**	**90% Upper (%)**
154.0	154.7	99.6	92.8	106.9
Reviewer's Calculations – AUC(0-t) (ng.hr/mL) (Food Effect)				
Tfast	**Tfed**	**Ratio (%)**	**90% Lower (%)**	**90% Upper (%)**
154.0	139.2	90.4	84.2	97.0
Reviewer's Calculations – AUC(0-inf) (ng.hr/mL) (Fasting)				
Tfast	**Rfast**	**Ratio (%)**	**90% Lower (%)**	**90% Upper (%)**
164.2	164.4	99.9	93.1	107.2
Reviewer's Calculations – AUC(0-inf) (ng.hr/mL) (Food Effect)				
Tfast	**Tfed**	**Ratio (%)**	**90% Lower (%)**	**90% Upper (%)**
164.2	151.2	92.1	85.8	98.8

Source: Clinical Pharmacology Reviewer's Analysis
Values for T_{fast}, R_{fast}, and T_{fed} are Geometric Least Squares Means
Applicant-provided data from SAS files were analyzed for bioequivalence using Phoenix 64 Software by Certara.

Table 11. Reviewer Summary of Bioequivalence Analyses for Piperazine N-Desmethyl Sildenafil Excluding Unreliable Data Identified by OSIS

Reviewer's Calculations – Cmax (ng/mL) (Fasting)				
Tfast	**Rfast**	**Ratio (%)**	**90% Lower (%)**	**90% Upper (%)**
33.8	32.4	104.4	95.4	114.2
Reviewer's Calculations – Cmax (ng/mL) (Food Effect)				
Tfast	**Tfed**	**Ratio (%)**	**90% Lower (%)**	**90% Upper (%)**
33.8	16.8	49.5	45.4	54.1
Reviewer's Calculations – AUC(0-t) (ng.hr/mL) (Fasting)				
Tfast	**Rfast**	**Ratio (%)**	**90% Lower (%)**	**90% Upper (%)**
151.5	149.2	101.5	94.7	108.7
Reviewer's Calculations – AUC(0-t) (ng.hr/mL) (Food Effect)				
Tfast	**Tfed**	**Ratio (%)**	**90% Lower (%)**	**90% Upper (%)**
151.5	139.2	91.9	85.8	98.3
Reviewer's Calculations – AUC(0-inf) (ng.hr/mL) (Fasting)				
Tfast	**Rfast**	**Ratio (%)**	**90% Lower (%)**	**90% Upper (%)**
161.0	158.1	101.8	95.1	109.1
Reviewer's Calculations – AUC(0-inf) (ng.hr/mL) (Food Effect)				
Tfast	**Tfed**	**Ratio (%)**	**90% Lower (%)**	**90% Upper (%)**
161.0	151.1	93.9	87.7	100.4

Source: Clinical Pharmacology Reviewer's Analysis
Values for T_{fast}, R_{fast}, and T_{fed} are Geometric Least Squares Means
Applicant-provided data from SAS files were analyzed for bioequivalence using Phoenix 64 Software by Certara.

4.2 PROPOSED LABELING

The Sponsor's proposed labeling is included on the following pages.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BRIANNA M COTE
06/11/2021 04:22:14 PM

MANOJ KHURANA
06/11/2021 07:14:22 PM