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2.7.1. Summary of Biopharmaceutics and Associated Analytical Methods

Tadalafil (IC351, LY450190) is marketed globally as Cialis®. The bioavailability, bioequivalence, and factors affecting bioavailability of tadalafil were previously evaluated in 5 biopharmaceutics studies (H6D-MC-LVBT [LVBT], [redacted] H6D-EW-LVCA [LVCA], H6D-EW-LVBX [LVBX], and H6D-EW-LVDL [LVDL]) involving 99 healthy adult subjects. The effect of food on absorption was previously evaluated in Study LVBT, as well as in three additional clinical pharmacology studies (H6D-EW-LVAL [LVAL], H6D-EW-LVDQ [LVDQ], H6D-EW-LVAI [LVAI]. One new food effect study was conducted to support the PAH indication (H6D-EW-LVHO [LVHO]) involving a total of 72 healthy adults. In addition, pertinent information about the bioavailability of tadalafil was obtained from the [^{14}C] Study H6D-LC-LVAA [LVAA] in 6 healthy adult subjects (Section 2.7.2.2.2.1).

Key study findings are as follows:

- The relative oral bioavailability of the tablet formulation of tadalafil compared with an oral suspension is 86% (range: 62% to 147%) based on the area under the concentration-time curve from time 0 to infinity ($AUC_{(0-\infty)}$).
- The radiolabeled dose recovered from the urine and as metabolites from feces indicates that the upper limit on the extent of systemic absorption of drug-related substance from a solution approximates 81%.
- [redacted]
- The bioequivalence across 2.5-, 5-, 10-, and 20-mg tablets has been established. Therefore, these tablet strengths can be used interchangeably to achieve the same total oral dose and systemic exposure.
- Food does not affect the rate or extent of tadalafil absorption with tadalafil dosing up to and including 40 mg.

2.7.1.1. Background and Overview

Tadalafil is an indole derivative with selective phosphodiesterase type 5 (PDE5) inhibitory action (Figure 2.7.1.1). Tadalafil drug substance is practically insoluble in water but demonstrated high intestinal permeability in an in vitro study using colonic carcinoma (Caco-2) cells. These properties of tadalafil support a Class 2 classification in the Biopharmaceutics Classification System (BCS).

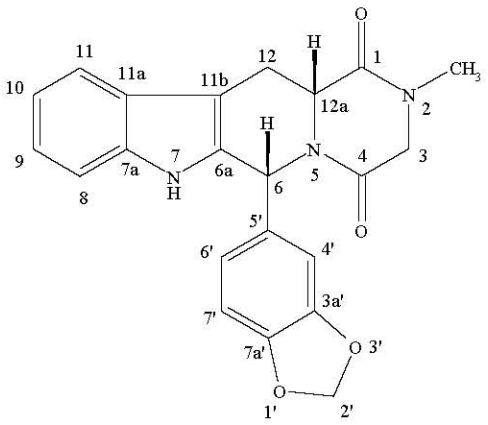


Figure 2.7.1.1. Tadalafil structure.

The designation as BCS Class 2 predicts that the oral bioavailability of tadalafil may be affected by factors that affect the dissolution or the solubility of the drug or drug product. Therein, drug substance and/or formulation chemical or physical characteristics that can potentially affect the absorption profile (for example, drug substance and/or particle size) have been evaluated and their effect on bioavailability have been minimized through formulation changes. Finally, drug product performance has been characterized in many different in vitro and in vivo biopharmaceutics studies to ensure that an optimal drug product is available for commercial manufacture.

2.7.1.1.1. Formulation Development Process Overview

The formulations used during the development of tadalafil fall into 5 categories: a suspension; a solution; coprecipitate tablets; [redacted]; and commercial product prepared with micronized crystalline tadalafil.

[redacted] An amorphous suspension formulation was investigated initially because early experiments in dogs indicated that crystalline tadalafil exhibited poor bioavailability. [redacted]

Therefore, a coprecipitate [redacted] (coprecipitate tablet) was investigated. The coprecipitate tablet exhibited bioavailability characteristics similar to amorphous suspension in dogs and was used in initial clinical pharmacology studies and Phase 2 studies for the erectile dysfunction indication; [redacted]

[redacted] Therefore, a crystalline drug tablet formulation utilizing micronized tadalafil, [redacted] was developed. [redacted] The crystalline drug tablet exhibited rapid absorption and good stability, and consequently it was selected as the formulation for Phase 3 clinical studies, the majority of clinical pharmacology studies, and as the commercial product (Cialis tablets). Because the commercial formulations of 2.5-, 10-, and 20-mg tablets were used in the 5 clinical pharmacology and the 2 pivotal studies for pulmonary arterial hypertension (PAH), no additional biopharmaceutics studies have been conducted.

The formulation for the PAH commercial 20-mg tablets is based on the formulations for the approved Cialis tablets (2.5, 10, and 20 mg) and is provided in Table 2.7.1.1 below. The formulation for the 20-mg tablets for PAH is similar to that of the approved 20-mg Cialis tablet according to the FDA Guidance for Industry, "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations" (FDA 2003). The composition of the core tablet is the same for both tablets. The coated tablets are differentiated by color. To this end, the color mixture orange (PAH indication) contains the same excipients [redacted] as the Cialis color mixture yellow with the addition [redacted] of red iron oxide. [redacted] (Table 2.7.1.1).

2.7.1.1.1.1. Unit Formulae

Table 2.7.1.1 includes the unit formulae for the tadalafil (yellow) 2.5-, 10-, and 20-mg tablets used in clinical trials and the proposed 20-mg tablet (orange).

Table 2.7.1.1. Unit Formulae

Ingredient	Quantity (mg/tablet)			
Active Ingredient	Tadalafil (yellow)	Tadalafil (yellow)	Tadalafil (yellow)	Tadalafil[a] (orange)
Tadalafil	2.500	10.000	20.000	20.000
Other Ingredients (Granulation)				
Lactose Monohydrate	[redacted]			
Lactose Monohydrate (Spray Dried)				
Hydroxypropyl Cellulose (Extra Fine [EF])				
Croscarmellose Sodium				
Hydroxypropyl Cellulose (EF)				
Sodium Lauryl Sulfate				
Outside Powders				
Microcrystalline Cellulose (Granular-102)				
Croscarmellose Sodium				
Magnesium Stearate (Vegetable)				
Total (Core)				
Film Coating				
Color Mixture Yellow (32K12891)				
Color Mixture Yellow (32K9203)				
Color Mixture Yellow (32K12884)				
Color Mixture Yellow (32K97462)				
Polishing				
Talc[b]				

a Tadalafil orange tablets were not used in clinical trials.

b [redacted]

2.7.1.1.1.2. Manufacturing Process

[redacted]

[redacted]

2.7.1.1.1.3. Lots Used in Clinical Studies

Table APP.2.7.1.4 includes a list of the clinical trial tablet lots used in clinical studies supporting this submission. Table APP.2.7.1.5 provides a cross-reference for the clinical trial drug product lots used in each of the relevant clinical studies.

2.7.1.1.2. Approach and Rationale for Biopharmaceutics Strategy

Four dose strengths of the tadalafil tablet formulations have been used in clinical pharmacology studies (2.5, 5, 10, and 20 mg). As they are not quantitatively identical formulations, bioequivalence between the four tablet strengths was investigated. Two studies were conducted in healthy male subjects to determine the relative bioavailability across the 2.5- to 20-mg tablets. The 2.5-, 5-, and 10-mg tablets using the 10-mg tablet as a reference formulation were compared in Study H6D-EW-LVBX original New Drug Application), and the 10- and 20-mg tablets were evaluated using the 20-mg tablet as a reference in Study H6D-EW-LVDL. The 2.5-, 5-, and 10-mg tablets and the 10- and 20-mg tablets were bioequivalent. Therefore, these tablet strengths can be used interchangeably to achieve the same total oral dose and systemic exposure. For studies specifically conducted for the PAH indication, 40-mg tadalafil was administered as two 20-mg tablets.

Because it is recognized that food can influence both the rate and extent of drug bioavailability, clinical studies of tadalafil have included pharmacokinetic assessments in both fed and fasting states for doses of 10, 20, and 40 mg.

2.7.1.1.3. Overview of Analytical Methods

The current validated analytical methods for the analysis of tadalafil, methylcatechol (unconjugated), and total methylcatechol (unconjugated methylcatechol and glucuronide of the methylcatechol) in human plasma are detailed in the initial submission for tadalafil (Erectile Dysfunction indication) and are summarized below. A list of the determination methods employed in each study is presented in Appendix 2.7.1.4 (Table APP.2.7.1.l).

ADME Report 62 Measurement of Tadalafil Concentrations in Human Plasma

Following solid-phase extraction, tadalafil concentrations in human plasma were determined using a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) method. [redacted]

ADME Report 81 Measurement of Tadalafil and the Methylcatechol Metabolite in Human Plasma

Following solid phase extraction, concentrations of tadalafil and the methylcatechol (unconjugated) metabolite in human plasma were determined with a validated LC/MS/MS method. [redacted]

ADME Report 84 Measurement of Total Methylcatechol Metabolite Concentrations in Hydrolyzed Human Plasma

As no analytical standard could be synthesized for the methylcatechol glucuronide, the main metabolite in human plasma, this metabolite was not measured directly. Total methylcatechol concentrations represent both unconjugated and glucuronide conjugate and was measured in plasma incubated with β-glucuronidase to hydrolyze glucuronide conjugates. As the unconjugated metabolite has been shown to generally represent less than 10% of the corresponding glucuronide conjugate in human plasma, total methylcatechol concentrations were used to determine the pharmacokinetic parameters of the major metabolite. Plasma samples were incubated with β-glucuronidase prior to solid-phase extraction and concentrations of the total methylcatechol metabolite were determined using a validated LC/MS/MS method. [redacted]

2.7.1.2. Summary Results of Individual Studies

This section provides details regarding the key studies that demonstrated bioequivalence between the 2.5-, 5-, and 10-mg tablet strengths (Study LVBX) and between 10 and 20 mg (Study LVDL). Other relative bioavailability studies included the effect of food (Study LVAL, Study LVDQ, and Study LVHO), and effect of dosing time (Study LVAI). The full clinical study reports (CSRs) for all bioequivalence and relative bioavailability studies are included in the original application (ED indication) for tadalafil, except that for Study LVHO, which is provided in Module 5 of this application. Table 2.7.1.2 provides an index of biopharmaceutics studies.

Table 2.7.1.2. Index of Biopharmaceutic Studies and Analyses

Brief Description of Study	Trial Alias
Absolute Bioavailability	
Bioavailability of oral suspension and tablet (100 mg)	LVBT
[^{14}C]tadalafil, 100 mg, single oral dose	LVAA
Relative Bioavailability and Bioequivalence	
Relative bioavailability and food effect of oral suspension and tablet	LVBT
Relative bioavailability of 3 formulations: KIT [redacted] coprecipitate	LVAH
[redacted]	[redacted]
Relative bioequivalence of 3 tablet strengths and dose proportionality of tadalafil PK administered at 4 dose strengths (2.5, 5, 10, and 20 mg), market image formulation	LVBX
Relative bioavailability of 2 dose strengths (10 and 20 mg) tablets, market image formulation	LVDL
Food Effect	
Food effect, 10 mg market image formulation	LVAL
Food effect, 20 mg market image formulation	LVDQ
Food effect, and evening dosing, 10 mg market image formulation	LVAI
Food effect, 40 mg commercial formulation	LVHO

Abbreviation: KIT = market image; PK = pharmacokinetics.

2.7.1.2.1. Absolute Bioavailability

Tadalafil has very low aqueous solubility, which precluded the formulation of a physically stable injectable solution for an absolute bioavailability study. Therefore, the relative oral bioavailability of tadalafil was determined by comparing exposure after tablet and oral suspension (Study LVBT). Additionally, inferences based upon the disposition of [^{14}C]tadalafil (Study LVAA, Section 2.7.2.2.2.1) provide estimates of the extent of systemic absorption from an oral solution. Brief narratives are presented below.

LVBT **A Study to Investigate the Effect of Food and the Relative Bioavailability of Tadalafil Administered as a Tablet and an Oral Suspension**

This was an open-label, 3-way crossover study conducted in 13 healthy male subjects (23 to 48 years old) to determine the relative bioavailability of coprecipitate tablets relative to the oral suspension. A secondary objective included a pilot assessment of the effect of food on rate and extent of tadalafil absorption.

Results and Conclusions: The relative bioavailability of the 100-mg tablet formulation was 86% of that of 100-mg oral suspension based upon $AUC_{(0-\infty)}$. The maximum plasma concentration (C_{max}) for the tablets was 68% of that observed following administration of the suspension in the fasted state.

LVAA **[^{14}C]Tadalafil (LY450190): Disposition after Oral Administration**

This was an open-label, inpatient study in 6 healthy adult male subjects (23 to 56 years old) to examine the metabolism, absorption, distribution, and excretion of tadalafil. Under fasting conditions, subjects received a single oral dose of approximately 100-mg [^{14}C]tadalafil administered as a polyethylene glycol 400 (PEG 400) solution.

Results and Conclusions: Approximately 97% of the radiolabeled dose was recovered in urine and feces within 312 hours of dosing. The 36% recovered in the urine indicated that at least 36% of the dose was systemically absorbed as tadalafil and/or metabolites. Approximately 45% of the radioactivity appeared in feces collected 48 to 312 hours after dosing. Analysis of fecal extracts showed the majority of radioactivity excreted after 24 hours was accounted for by metabolites of tadalafil, suggesting this radioactivity represented biliary secretion of the metabolites rather than unabsorbed tadalafil. As it is reasonable to assume most unabsorbed radioactivity would have been eliminated in the feces in the 0 to 48 hour collection period, the 45% recovered after 48 hours may represent drug-related material secreted into the bile after systemic absorption. Thus, a hypothetical upper limit on the extent of systemic absorption of drug-related (radiolabel) substance from a PEG 400 solution is approximately 81% (36% + 45%). The disposition of tadalafil is further summarized in the Summary of Clinical Pharmacology (Section 2.7.2.2.2.1).

2.7.1.2.2. Relative Bioavailability and Bioequivalence

To select the best formulation to commercialize, pharmacokinetics data from two test formulations (crystalline drug tablet and [redacted] were compared with data from the coprecipitate formulation (Study LVAH). [redacted] Moreover, two more studies (Studies LVBX and LVDL) evaluated the bioequivalence of tadalafil tablets across four dose strengths (2.5, 5, 10, and 20 mg). The effect of food or dose timing was evaluated in an additional four relative bioavailability studies. Table APP.2.7.1.2 and Table APP.2.7.1.3 (Appendix 2.7.1.4) summarize the study designs and the pharmacokinetic results by study. Brief narratives describing each study and the study results are presented below.

LVAH **A Study to Examine the Safety, Tolerability, and Pharmacokinetics of Three Formulations of Tadalafil (LY450190): KIT, [redacted] and Coprecipitate**

This was an open-label, balanced, randomized, 3-way crossover study in 18 healthy adult males (21 to 60 years old) to compare the pharmacokinetics of 3 different formulations (crystalline drug tablet [KIT], coprecipitate tablet, and [redacted] of tadalafil. A

single oral dose of 10-mg tadalafil was administered after an overnight fast on three separate occasions with a 7-day washout between doses.

Results and Conclusions: The 90% confidence interval (CI) for the ratio of the geometric mean of $AUC_{(0-\infty)}$ (crystalline drug tablets/coprecipitate tablets, and [redacted] coprecipitate tablets) was between 0.80 and 1.25, and therefore, both the crystalline drug tablets and [redacted] were bioequivalent with the coprecipitate formulation based on this parameter. In contrast, the geometric means of C_{max} were higher for crystalline drug tablets and [redacted] than for coprecipitate tablets by 27% and [redacted] respectively, and the upper limit of the 90% CI of the ratio exceeded 1.25. As the crystalline drug tablets demonstrated lower intersubject variability in $AUC_{(0-\infty)}$ and C_{max}, and the time to maximum plasma concentration (t_{max}) was consistent (2 to 6 hours postdose) compared to other formulations, the crystalline drug tablets were chosen as the commercial product (market image).

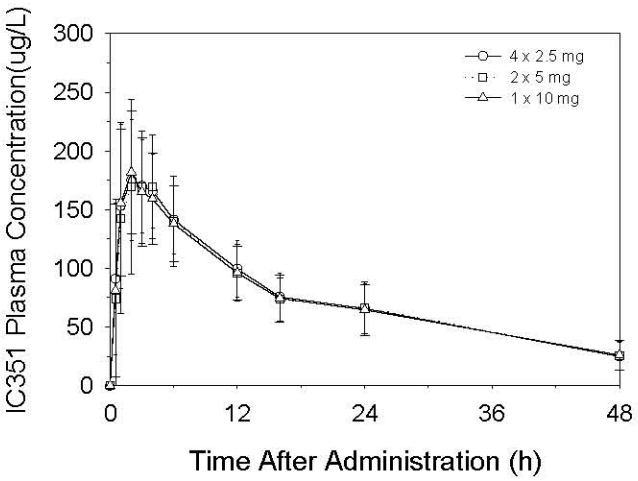
[redacted]

LVBX **A Study in Healthy Subjects to Determine the Relative Bioequivalence of Three Tablet Strengths (4 × 2.5 mg versus 2 × 5 mg versus 1 × 10 mg) of Tadalafil and the Dose Proportionality of Tadalafil Pharmacokinetics when Administered at Four Dose Levels (2.5, 5, 10, and 20 mg)**

This was a single (subject)-blind, randomized, crossover study conducted in two parts (Parts A and B), each of which involved a separate group of subjects. In both Part A and Part B, tadalafil tablets were administered in the fasted state in the morning as a single oral dose.

Part A was a 3-period crossover design conducted in 24 healthy adult subjects (12 males and 12 females; 21 to 55 years old) to assess the relative bioequivalence of three market image tablet strengths of tadalafil (2.5, 5, and 10 mg) administered at a dose level of 10 mg. Only Part A is discussed in this section. Part B is detailed in Section 2.7.2.2.2.1 of this dossier.

Results and Conclusions: Figure 2.7.1.2 shows the profiles of tadalafil plasma concentrations after single oral administration of 2.5-mg tablet × 4 tablets, 5-mg tablet × 2 tablets and 10-mg tablet × 1 tablet.



Abbreviation: h = hours.
N=24 in each dose strength
µg/L is equivalent to ng/Ml.
Source: LVBX CSR Figure11.1

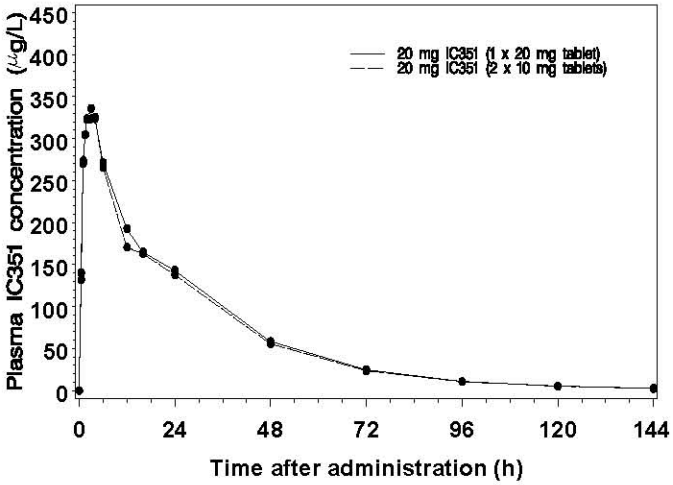
Figure 2.7.1.2. Arithmetic mean (± standard deviation [SD]) plasma concentration-time profiles of tadalafil following oral administration of a single 10-mg dose as three tablet strengths (4 × 2.5 mg, 2 × 5 mg, and 1 × 10 mg) (0-48 hours).

The 90% CI of the ratio of geometric least squares (LS) means of $AUC_{(0-\infty)}$ and C_{max} of 2.5-mg tablet × 4 tablets and 5-mg tablet × 2 tablets as compared to the reference (10-mg tablet × 1 tablet) were contained within the equivalence limits of 0.80 to 1.25, indicating bioequivalence of these tablets of different dose strengths.

LVDL A Study to Determine the Relative Bioavailability of Two Dose Strengths of Tadalafil (LY450190) 20- to 10-mg Tablets

This was an open-label, randomized, 2-period crossover study conducted in 20 healthy adult males (27 to 64 years old) to assess the relative bioavailability of two different market image tadalafil dose strengths (10-mg tablet × 2 tablets and 20-mg tablet × 1 tablet). Tadalafil tablets were administered in the fasted state in the morning as single 20-mg oral doses.

Results and Conclusions: Figure 2.7.1.3 shows the profiles of plasma tadalafil concentrations after single oral administration of 10-mg tablet × 2 tablets and 20-mg tablet × 1 tablet.



Abbreviation: h = hours.
N=20 in each dose strength
µg/L is equivalent to ng/mL
Source: LVDL CSR Figure 11.2

Figure 2.7.1.3. Tadalafil mean plasma concentration-time profiles following a single 20-mg oral dose of tadalafil administered as 20-mg tablet × 1 tablet or 10-mg tablet × 2 tablets.

The 90% CI of the ratio of geometric LS means of $AUC_{(0-\infty)}$ and C_{max} of 20-mg tablet × 1 tablet as compared to the reference (10-mg tablet × 2 tablets) were contained within the equivalence limits of 0.80 to 1.25, indicating bioequivalence of these tablets with different dose strengths.

2.7.1.2.3. Food Effect and Dose Timing Studies

For BCS Class 2 drug products such as tadalafil, food effects may result from a complex combination of factors that influence the in vivo dissolution of the drug product and absorption of the drug substance. Therefore, the effect of food on the pharmacokinetics of tadalafil after single oral dose administration of 10-mg tadalafil (Study LVAL) and 20-mg (Study LVDQ) was evaluated. Subsequently, to specifically support the PAH application, an additional study (LVHO) was conducted to assess the effect of food on a 40-mg dose. The effect of dosing time and of food on pharmacokinetics was evaluated following single oral administration of 10-mg tadalafil in (Study LVAI). A summary of pharmacokinetic studies that investigated the effect of food is presented in Appendix 2.7.1.4 (Table APP.2.7.1.3).

LVAL **A Study in Healthy Subjects to Assess the Effect of Food on the Pharmacokinetics of Tadalafil Administered as a Single Oral Dose of 10 mg (Market Image Formulation)**

The was an open-label, randomized, 2-period crossover study conducted in 16 healthy adult subjects (8 males and 8 females; 24 to 64 years old) to assess the effect of food on the pharmacokinetics of tadalafil. On two separate occasions, each subject received a single oral administration of 10-mg tadalafil in the fasted state in the morning or within 5 minutes after high-fat breakfast (approximately 50% of total caloric content of the meal). There was an interval of at least 10 days between dosing in each period.

Results and Conclusions: Statistical analysis indicated that the ratio of geometric LS means (90% CI) of $AUC_{(0-\infty)}$ and C_{max} (after breakfast or fasted) were 0.95 (0.84 to 1.07) and 0.96 (0.82 to 1.13), respectively. The $AUC_{(0-\infty)}$ and C_{max} were equivalent for tadalafil when administered in the fasted and fed (high fat) states, with the 90% CI for the ratios falling within the equivalence limits of 0.80 to 1.25 for AUC and 0.70 to 1.43 for C_{max}. The results indicate that there is no effect of food on tadalafil pharmacokinetics.

LVDQ **A Study in Healthy Subjects to Assess the Effect of Food on the Pharmacokinetics of Tadalafil Administered as a Single Oral Dose of 20 mg (Market Image Formulation)**

The was an open-label, randomized, 2-period crossover study conducted in 18 healthy adult subjects (4 males and 14 females; 19 to 62 years old) to assess the effect of food on the pharmacokinetics of tadalafil (market image tablet). On two separate occasions, each subject received single oral 20-mg tadalafil dose in the fasted state in the morning or within 5 minutes after a high-fat breakfast (approximately 50% of total caloric content of the meal). An interval of at least 14 days separated dosing in each treatment period.

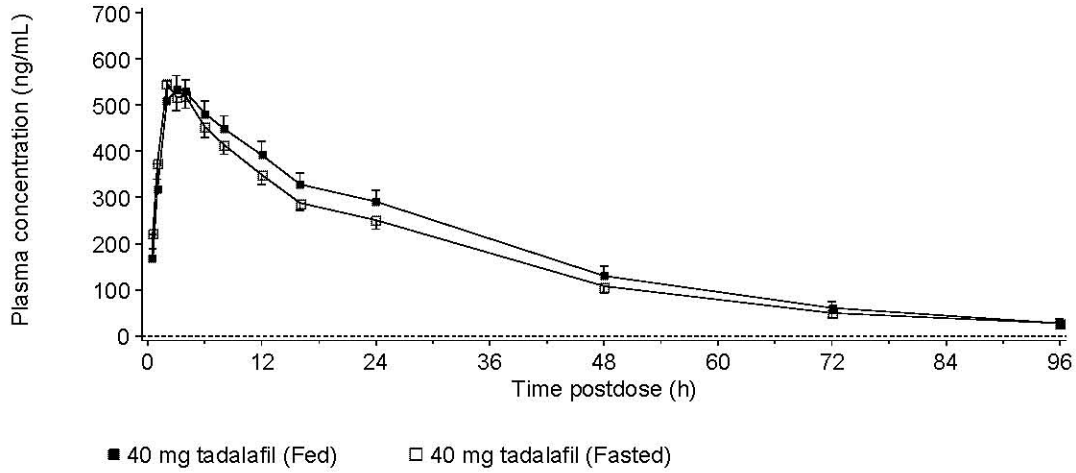
Results and Conclusions: Statistical analysis indicated that the ratio of geometric LS means (90% CI) of $AUC_{(0-\infty)}$ and C_{max} (fed/fasted) were 1.08 (1.02, 1.15) and 1.16 (1.07, 1.26), respectively. The $AUC_{(0-\infty)}$ and C_{max} were equivalent for tadalafil when administered in the fasted and fed (high fat) states, with the 90% CI for the ratios falling within the equivalence limits of 0.80 to 1.25 for AUC and 0.70 to 1.43 for C_{max}. Therefore, there is no effect of food on pharmacokinetics for administration of tadalafil 20 mg.

LVHO **A Study in Healthy Subjects to Assess the Effect of Food on the Pharmacokinetics of Tadalafil Administered as a Single Oral Dose of 40 mg**

This was an open-label, randomized, 2-period crossover study conducted in 15 healthy subjects (9 male and 6 female; 21 to 61 years old) to assess the effect of food on the pharmacokinetics of tadalafil. On one occasion during each of two treatment periods, subjects received a single 40-mg oral dose (2 × 20-mg tablets) of tadalafil in the fasted

state and within 30 minutes of starting an FDA-defined high-fat breakfast. An interval of at least 7 days separated dosing in each treatment period.

Results and Conclusions: Figure 2.7.1.4 shows the profiles of plasma tadalafil concentrations after single oral administration of 40 mg in fasting and fed conditions The ratio of geometric LS means (90% CI) for $AUC_{(0-\infty)}$ and C_{max} (fed/fasted) were 1.14 (1.05 to 1.22) and 1.07 (0.994 to 1.15), respectively. Statistical analysis indicated that AUC and C_{max} were equivalent for tadalafil when administered in the fasted and fed (high-fat) conditions, with the 90% CI for the ratios falling within the equivalence limits of 0.80 to 1.25 for AUC and 0.70 to 1.43 for C_{max}. There was no significant difference in t_{max} when tadalafil was administered with and without food. These findings are in agreement with the results of previous studies (LVAL and LVDQ) in which single oral doses of 10- and 20-mg tablets were administered and indicate bioavailability of tadalafil is equivalent irrespective of dietary condition. Therefore, tadalafil may be administered without regard to meals.



Abbreviations: h = hours; N = number of subjects; SEM = standard error of the mean.
Source: LVHO CSR Figure LVHO.7.1

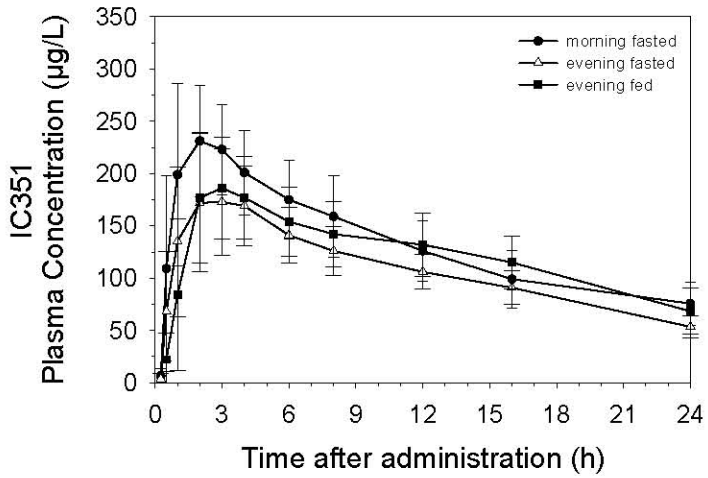
Figure 2.7.1.4. **Arithmetic mean (± SEM) plasma concentration-time profiles of tadalafil after oral administration of a single 40-mg dose in the fed (high fat) state (N=13) and in the fasted state (N=14) over 96 hours postdose.**

LVAI **A Study to Assess the Effect of Food and Evening Dosing on the Pharmacokinetics of Tadalafil**

The was an open-label, randomized, 3-period crossover study conducted in 12 healthy adult males (20 to 51 years old) to assess the effects of food and evening dosing on the pharmacokinetics of tadalafil. Each subject received a single oral 10-mg tadalafil dose in

the fasted state in the morning, in the fasted state in the evening, and within 5 minutes after a high-fat dinner (approximately 50% of total caloric content of the meal). An interval of at least 10 days separated dosing in each of the three treatment periods.

Results and Conclusions: Figure 2.7.1.5 shows the profiles of plasma tadalafil concentrations after single oral administration of 10-mg tadalafil in the fasted state in the morning, in the fasted state in the evening, and in the fed state in the evening.



Abbreviations: h = hours; SD = standard deviation.
N=12 in each condition
µg/L is equivalent to ng/mL
Source: LVAI CSR Figure 11.1

Figure 2.7.1.5. **Mean plasma concentration-time profiles of tadalafil after oral administration of a single 10-mg dose in the fasted state in the morning and evening and in the fed state (high fat) in the evening (arithmetic mean ±SD).**

The $AUC_{(0-\infty)}$ and C_{max} in the fasted state in the evening were about 19% and 21%, respectively lower than in the fasted state in the morning. The ratio of geometric LS means (90% CI) for $AUC_{(0-\infty)}$ and C_{max} (fasted in the evening/fasted in the morning) were 0.810 (0.727 to 0.903) and 0.793 (0.711 to 0.885), respectively. The 90% CI for $AUC_{(0-\infty)}$ was slightly less than the lower limit of the 90% CI of 0.8; whereas, the C_{max} was fully contained within the 0.70 to 1.43 limit. The LS means for $AUC_{(0-\infty)}$ were approximately 15% higher following evening dosing in the fed state compared to the fasted state. The ratio of geometric LS means (90% CI) for $AUC_{(0-\infty)}$ and C_{max} (fed evening/fasted evening) were 1.15 (1.04 to 1.28) and 1.03 (0.923 to 1.15), respectively, with 90% CI for C_{max} fully contained within the limits of 0.70 to 1.43 and that for AUC slightly extending beyond the upper limit of 1.25. The differences in tadalafil pharmacokinetics between treatments were small and were not considered to be of clinical significance.

2.7.1.3. Comparison and Analysis of Results across Studies

2.7.1.3.1. Bioequivalence

The comparative bioavailability of various formulations of tadalafil has been assessed during development. Four studies have compared bioavailability between solid dosage forms, and a fifth study (Study LVBT) compared the bioavailability of the tablet formulation with that of an oral suspension.

Table 2.7.1.3 lists the means and 90% CI based on comparisons of $AUC_{(0-\infty)}$ and C_{max} in Studies LVCA, LVAH, LVBX, and LVDL.

Table 2.7.1.3. Summary of Relative Bioavailability of Different Dose Strengths

Study (N)	Geometric Mean (% CV) of PK Parameter			Ratio of geometric LS means (90% CI)[a]	
	Dose [redacted]	C_{max} (µg/L)	$AUC_{(0-\infty)}$ (µg*h/L)	C_{max}	$AUC_{(0-\infty)}$
LVBX (N=24)	2.5 mg tablet x 4	190	4120	4x2.5 mg tablet / 1x10 mg tablet	
		[redacted]	[redacted]	1.03 (0.96, 1.10)	1.03 (0.97, 1.09)
	5 mg tablet x 2	196	4071	2x5 mg tablet / 1x10 mg tablet	
		[redacted]	[redacted]	1.06 (0.99, 1.14)	1.02 (0.96, 1.08)
	10 mg tablet x 1	184	4005	—	—
		[redacted]	[redacted]		
LVDL (N=20)	10 mg tablet x 2	346	8192	1x20 mg / 2x10mg	
		[redacted]	[redacted]	1.01 (0.940, 1.09)	1.02 (0.941, 1.11)
	20 mg tablet x 1	351	8383	—	—
		[redacted]	[redacted]		
LVAH (N=18)	Coprecipitate tablet 10 mg x 1	158	3936	Market Image tablet /Coprecipitate	
		[redacted]	[redacted]	1.27 (1.12, 1.45)	0.957 (0.889, 1.03)
	Market Image tablet 10 mg x 1	202	3767	[redacted]	
		[redacted]	[redacted]		

[redacted]

Abbreviations: $AUC_{(0-\infty)}$ = area under the concentration time curve from time 0 to infinity; C_{max} = maximum plasma concentration; CI = confidence interval; CV = coefficient of variation; LS = least squares; N = number of subjects.

[a] The ratio and corresponding confidence limits are back – transformed from the difference calculated on the log scale.

[redacted]

Source: LVBX CSR Tables 11.1, 11.2; LVDL CSR Tables 11.1, 11.2; [redacted]

[redacted]

The four tablet strengths in Studies LVBX and LVDL were bioequivalent based on $AUC_{(0-\infty)}$ and C_{max}. Point estimates and the 90% CI for these primary parameters between dose strengths have been within the range of 0.80 to 1.25.

2.7.1.3.2. Effect of Dosing Time and Food

The effect of food was evaluated after administration of 10-, 20-, and 40-mg tadalafil after breakfast (Studies LVAL, LVDQ, and LVHO) and administration of 10-mg tadalafil in the fed and fasted state in the evening (Study LVAI). Table 2.7.1.4 summarizes the results of these studies.

In Study LVDQ (20-mg tadalafil in the fed state in the morning), C_{max} was 16% higher in the fed state compared to the fasted state. In Study LVAI (10-mg tadalafil in the fed state in the evening), AUC was 15% higher in the fed state compared to the evening fasted state. Similarly, in the evaluation of 40 mg, mean values for both AUC and C_{max} were 14% and 7%, respectively, higher under fed conditions compared to fasted. Whereas, in Study LVAL (10-mg tadalafil in the fed state in the morning), C_{max} and AUC in the fed state were comparable to the fasted state. Overall, bioavailability and bioequivalence was demonstrated among formulations and dose-strengths when tadalafil was administered in fasting and fed conditions; therefore, there appeared to be no effect of food on administration of tadalafil.

Table 2.7.1.4. Summary of Food Effect Studies

	Tadalafil	Timing	PK Parameter	Geometric Mean		Ratio of geometric LS means (fed / fasted) (90% CI)[a]
				Fed	Fasted	
LVHO	40 mg (N=15)	morning	$AUC_{(0-\infty)}$ ((µg*h/L)	17386	15404	1.14 (1.05, 1.22)
			C_{max} (µg/L)	586	553	1.07 (0.994, 1.15)
LVAL	10 mg (N=16)	morning	$AUC_{(0-\infty)}$ (µg*h/L)	4905	5181	0.95 (0.84, 1.07)
			C_{max} (µg/L)	210	219	0.96 (0.82, 1.13)
LVDQ	20 mg (N=18)	morning	$AUC_{(0-\infty)}$ (µg*h/L)	6943	6419	1.08 (1.02, 1.15)
			C_{max} (µg/L)	345	297	1.16 (1.07, 1.26)
LVAI	10 mg (N=12)	evening	$AUC_{(0-\infty)}$ (µg*h/L)	4490	3894	1.15(1.04, 1.28)
			C_{max} (µg/L)	194	188	1.03(0.923, 1.15)

Abbreviations: $AUC_{(0-\infty)}$ = area under the concentration time curve from time 0 to infinity; C_{max} = maximum plasma concentration; CI = confidence interval; LS = least squares; N = number of subjects; PK = pharmacokinetic. Note: µg/L is equivalent to ng/mL.

[a] The ratio and corresponding confidence limits are back – transformed from the difference calculated on the log scale.

Source: LVHO CSR Table 7.1, 7.3, LVAL CSR Table 11.1, 11.2, LVDQ CSR Table 11.1, 11.2 and LVAI CSR Table 11.1, 11.3.

Differences in pharmacokinetics after administration in the morning and in the evening are known with numerous drugs (Nakano et al. 1984; Hla et al. 1992). However, in most cases and like that for tadalafil, the difference is not considered to be clinically significant. Regarding the effect of dosing time, C_{max} was 19% and AUC was 21% lower in the evening compared to the morning, under fasting conditions (Study LVAI). In Study LVAI, any differences were not considered to be clinically significant and any dose adjustment was not warranted.