

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-332**

**PHARMACOLOGY REVIEW(S)**

NDA 22332

REVIEW AND EVALUATION OF PHARMACOLOGY DATA

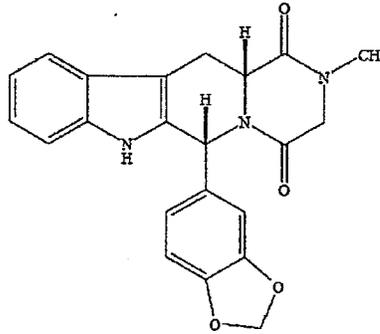
**SUBMISSION DATED:** July 23, 2008  
**CENTER RECEIPT DATE:** July 24, 2008  
**REVIEWER RECEIPT DATE:** July 24, 2008  
**REVIEW COMPLETION DATE:** March 5, 2009

**REVIEWER:** John Koerner, Ph.D.  
Senior Pharmacologist  
Division of Cardiovascular and Renal Products

**SPONSOR:** Eli Lilly and Company

**DRUG**

**Code Name:** LY450190  
**General/ Generic Name:** Tadalafil  
**Trade Name:** ADCIRCA  
**Empirical Formula:** C<sub>22</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub>  
**CAS Number:** 171596-29-5  
**Chemical Structure**



M.W. , 389.41

**PHARMACOLOGICAL CLASS:**  $\beta$ -carboline phosphodiesterase (PDE) type 5 inhibitor

**PROPOSED USE:** Treatment of pulmonary hypertension

**FORMULATION AND ROUTE OF ADMINISTRATION:**  film-coated, almond-shaped tablets containing 20 mg of tadalafil and inactive ingredients of lactose monohydrate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide, croscarmellose sodium, sodium lauryl sulfate, microcrystalline cellulose, talc, titanium dioxide, triacetin & magnesium stearate.

b(4)

**PROPOSED DOSING REGIME:** 40 mg daily oral dose

**Related Eli Lilly Applications:** NDA 21368, CIALIS for male erectile dysfunction  
IND 71871 for pulmonary hypertension.

b(4)

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## EXECUTIVE SUMMARY

Tadalafil, a PDE5 inhibitor, is proposed for the treatment of pulmonary hypertension in male and female patients, with a maximum recommended human dose of 40 mg/day. Tadalafil is presently marketed for treatment of male erectile dysfunction, with a maximum recommended human dose of 20 mg (single use) or 10 mg/day for daily use. Although the erectile dysfunction indication is limited to male use, nonclinical data for both males and females is summarized in the approved label, and includes reproductive toxicity, genotoxicity and carcinogenicity data. The agency agreed in a Pre-NDA meeting on January 15, 2008, that the nonclinical overview based on the erectile dysfunction application, along with a newly submitted nonclinical pharmacodynamic study showing efficacy in a rodent pulmonary hypertension model, provides sufficient nonclinical information for the present application.

The relationship between PDE5 inhibition and free plasma tadalafil concentrations ( $C_{max,free}$ ) in healthy human subjects suggests that inhibition of PDE5 was complete following oral doses of 10, 20 and 40 mg/day, i.e., the doses should be indistinguishable, at least at  $C_{max}$ . The same analysis performed with free plasma drug levels in patients given sildenafil suggests that PDE5 inhibition was incomplete at the approved dose of 20 mg tid, and even higher doses up to 80 mg, tid. Since free plasma drug levels may not accurately reflect drug concentration at the site of action, i.e., at PDE5, this analysis should be evaluated cautiously.

The only additional nonclinical study included with this NDA is a study evaluating the effects of tadalafil in a rodent model of pulmonary hypertension. In this study, tadalafil (10 mg/kg/day, po) was efficacious in rats with monocrotaline-induced pulmonary hypertension, both when given prior to, and after, development of pulmonary hypertension. Tadalafil had both functional and mortality benefits in this model, similar to the concurrent positive control, sildenafil (25 mg/kg/day, po).

As the maximum recommended human dose is higher for the pulmonary hypertension indication than the erectile dysfunction indication, animal to human exposure ratios need to be changed from the erectile dysfunction label. The sponsor provided, in an email dated February 25, 2009 (and later in submission 001; letter date 03/02/09) human exposure multiples based on the median steady state exposure ( $AUC_{ss}$ , 14825 ng.hr/ml) in pulmonary hypertensive patients given 40 mg/day (study LVGY). These ratios (multiples of human exposure) appear reasonable and are reflected in the modified label provided in this submission. (001; letter date 03/02/09).

This reviewer does not recommend any additional nonclinical studies. The sponsor's proposed label submitted in on March 2, 2009, (submission 001) with dose multiples modified to account for plasma exposures seen in pulmonary hypertensive patients, appears adequate. This reviewer does not recommend any additional label changes.

**Pharmacology Study**

Study Title: Effects of Tadalafil (LY450190) on Monocrotaline Pulmonary Hypertensive Rats

Key Findings: Tadalafil (10 mg/kg/day, po) was efficacious in a rodent model of pulmonary hypertension, both when given prior to, and after, development of pulmonary hypertension. Tadalafil had both functional and mortality benefits in this model, similar to the concurrent positive control, sildenafil (25 mg/kg/day, po).

Study Number: 030327

Report Status: Final and quality assured

Study Initiation Date: April 12, 2007

Study Facility:

b(4)

GLP Compliance: Yes

Animals: Male Sprague Dawley rats ~ CD (SD))

b(4)

Number/dose: 5 for Prevention Study (Experiment 1)  
20 for Treatment Study (Experiment 2)

Age: 6 weeks

Body weight: 166-204 g

Drug: Tadalafil (LY450190)

Lot Number: A264763

Dose: 0.5, 2.5, and 10.0 mg/kg/day, p.o.

Vehicle: 10% gum arabic in water

Reference Drug: Sildenafil citrate

Lot Number: 0601011360s

Dose: 25 mg/kg/day, po given as 2 daily doses

Vehicle: 0.9% saline

**Methods**

The sponsor performed 2 studies in rats with pulmonary hypertension induced by a single 60 mg/kg, sc dose of monocrotaline (MCT). The first study (Experiment 1: pulmonary hypertension prevention study) evaluated the effects of tadalafil on the development of pulmonary hypertension. The second study (Experiment 2: treatment study) evaluated the effect of tadalafil on survival following development of pulmonary hypertension. In both studies, a separate group of rats given sildenafil (25 mg/kg/kg, po) served as a concurrent positive control. The sponsor based dose selection of tadalafil (high dose of 10 mg/kg) on similarity of AUC in rats given this dose to the AUC seen in humans given the proposed therapeutic dose of 40 mg/day, po. The dose of sildenafil (25 mg/kg/day, po) used in this study was shown previously to inhibit monocrotaline-induced pulmonary hypertension in rats.<sup>1</sup>

<sup>1</sup> Itoh T, et al. A combination of oral sildenafil and beraprost ameliorates pulmonary hypertension in rats. Am. J. Respir. Crit. Care Med. 168: 34-38, 2004

**Experiment 1: Pulmonary hypertension prevention study**

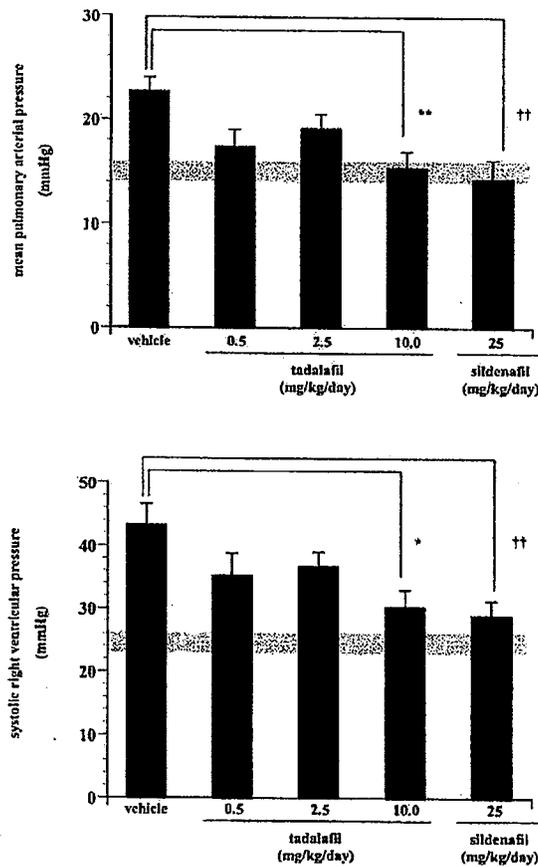
Rats were given tadalafil or sildenafil for 3 weeks starting on the day of MCT injection. On day 21, the last day of dosing, animals were anesthetized, a thoracotomy was performed, and pulmonary hemodynamics (pulmonary arterial and right ventricular pressures), mean arterial blood pressure, heart rate, mixed venous blood gases (pO<sub>2</sub>, pCO<sub>2</sub> and pH), right and left ventricular cardiac weights, and plasma and lung cyclic guanosine monophosphate (cGMP) levels were measured.

**Experiment 2: Treatment study**

Pulmonary hypertension was confirmed in a satellite group of rats by measurement of pulmonary arterial blood pressure, right atrial pressure and right ventricular weights at 3 weeks after MCT injection. Main treatment animals were then given tadalafil or sildenafil for 3 weeks starting 3 weeks after administration of MCT. The effect of drugs on median survival time over this 3 week treatment period was determined. On day 41 (20 days after starting drug treatment), surviving animals were anesthetized, a thoracotomy was performed, and right ventricular and left ventricular cardiac weights, arterial blood gases (pO<sub>2</sub>, PCO<sub>2</sub> and pH), and pulmonary and plasma cGMP levels were measured.

**Results**

**Experiment 1: Tadalafil (10 mg/kg/day) and sildenafil (25 mg/kg/day) reduced mean pulmonary arterial and right ventricular systolic pressures compared to vehicle control.**



Tadalafil (10 mg/kg/day) did not affect right ventricular weight corrected for body weight and as a fraction of left ventricular weight. In contrast, sildenafil (25 mg/kg/day) reduced these indices compared to vehicle.

Group	Dose mg/kg/day	Number of rats	RV g	LV+S g	BW g	RV/BW g/kg	(LV+S)/BW g/kg	RV/(LV+S) g/g
normal	-	5	0.1178 ± 0.0295	0.6024 ± 0.1154	327.41 ± 27.57	0.36 ± 0.07	1.84 ± 0.26	0.19 ± 0.01
vehicle	-	5	0.1469 ± 0.0216	0.5601 ± 0.0772	285.20 ± 36.65	0.52 ## ± 0.07	2.00 ± 0.49	0.27 # ± 0.05
tadalafil	0.5	5	0.1352 ± 0.0198	0.5581 ± 0.0858	292.19 ± 45.17	0.47 ± 0.07	1.93 ± 0.29	0.24 ± 0.02
	2.5	5	0.1503 ± 0.0477	0.5563 ± 0.0662	291.32 ± 15.77	0.52 ± 0.17	1.90 ± 0.16	0.27 ± 0.09
	10.0	5	0.1356 ± 0.0485	0.6016 ± 0.1091	300.19 ± 15.27	0.45 ± 0.14	2.00 ± 0.32	0.22 ± 0.05
sildenafil	25	5	0.1150 ± 0.0253	0.5765 ± 0.0802	311.19 ± 22.53	0.37 † ± 0.08	1.85 ± 0.19	0.20 † ± 0.03

Cardiac weight measurement was performed on Day 21 (Day 1 denotes the day of MCT injection).

Drugs were orally administered from Day 1 to Day 21. Tadalafil was administered once a day, but sildenafil was twice a day.

Data are shown as mean ± S.D.

Vehicle group vs normal group; Student's t-test (RV/BW) or Aspin-Welch's t-test (RV/(LV+S)), #: p < 0.05, ##: p < 0.01

Sildenafil group vs vehicle group; Student's t-test, †: p < 0.05

Definition of abbreviations:

RV = weight of right ventricle; LV+S = weight of left ventricle and septum; BW = body weight;

RV/BW = ratio of RV to BW; (LV+S)/BW = ratio of LV+S to BW; RV/(LV+S) = ratio of RV to LV+S

Tadalafil (10 mg/kg/day) and sildenafil (25 mg/kg/day) increased lung levels of cGMP compared to vehicle.

Group	Dose mg/kg/day	Number of rats	plasma cGMP pmol/mL	lung cGMP pmol/wg
normal	-	5	1.45 ± 0.64 (2)	46 ± 17
vehicle	-	5	5.90 ± 3.68 (3)	50 ± 11
tadalafil	0.5	5	11.98 ± 13.50	81 ± 51
	2.5	5	32.60 ± 37.68	118 ± 40
	10.0	5	17.56 ± 9.45	135 * ± 53
sildenafil	25	5	46.96 ± 74.56	150 †† ± 33

Extraction of plasma or lung tissue was performed on Day 21 (Day 1 denotes the day of MCT injection).

Drugs were orally administered from Day 1 to Day 21. Tadalafil was administered once a day, but sildenafil was twice a day.

Data are shown as mean ± S.D.

Each value in parenthesis is represented as number of rats.

Tadalafil group vs vehicle group; Dunnett's test, \*: p < 0.05

Sildenafil group vs vehicle group; Student's t-test, ††: p < 0.01

Definition of abbreviations:

cGMP = cyclic guanosine 3', 5'-monophosphate; wg = wet weight

Neither tadalafil (10 mg/kg/day) nor sildenafil (25 mg/kg/day) altered mixed venous blood gases compared to vehicle.

Group	Dose mg/kg/day	Number of rats	pH	pCO <sub>2</sub> mmHg	pO <sub>2</sub> mmHg
normal	-	5	7.45 ± 0.02	38 ± 3	38 ± 3
vehicle	-	5	7.41 ## ± 0.02	41 ± 3	35 ± 2
tadalafil	0.5	5	7.37 ± 0.05	45 ± 2	33 ± 6
	2.5	5	7.41 ± 0.03	43 ± 5	33 ± 7
	10.0	5	7.42 ± 0.02	41 ± 3	36 ± 6
sildenafil	25	5	7.38 ± 0.06	43 ± 6	35 ± 8

Blood gas analysis was performed on Day 21 (Day 1 denotes the day of MCT injection).

Drugs were orally administered from Day 1 to Day 21. Tadalafil was administered once a day, but sildenafil was twice a day.

Data are shown as mean ± S.D.

Vehicle group vs normal group; Student's t-test, ##: p < 0.01

Experiment 2: Development of pulmonary hypertension was confirmed in a satellite group of animals given MCT, as shown by elevated pulmonary arterial and right atrial systolic blood pressures, and right ventricular weight (corrected for body weight and left ventricular weight) at 21 days after MCT administration.

#### Mean Pulmonary Arterial Pressure

Group	Dose mg/kg	Number of rats	MBP mmHg	MPAP mmHg	HR BPM
normal	-	5	55.2 ± 8.2	10.2 ± 1.3	334 ± 94
MCT-treated	60	5	60.7 ± 5.7	21.1 ## ± 2.2	383 ± 70

Hemodynamic measurement was performed on Day 21~Day 23 (Day 1 denotes the day of MCT injection).

Data are shown as mean ± S.D.

MCT-treated group vs normal group; Student's t-test, ##: p < 0.01

Definition of abbreviations:

MBP = mean systemic arterial pressure; MPAP = mean pulmonary arterial pressure; HR = heart rate

#### Right Ventricular Systolic Pressure

Group	Dose mg/kg	Number of rats	MBP mmHg	SRVP mmHg	HR BPM
normal	-	5	59.8 ± 8.3	22.6 ± 4.4	355 ± 97
MCT-treated	60	5	64.3 ± 10.6	40.2 ## ± 2.7	415 ± 49

Hemodynamic measurement was performed on Day 21~Day 23 (Day 1 denotes the day of MCT injection).

Data are shown as mean ± S.D.

MCT-treated group vs normal group; Student's t-test, ##: p < 0.01

Definition of abbreviations:

MBP = mean systemic arterial pressure; SRVP = systolic right ventricular pressure; HR = heart rate

Right Ventricular Weight

Group	Dose mg/kg	Number of rats	RV g	LV+S g	BW g	RV/BW g/kg	(LV+S)/BW g/kg	RV/(LV+S) g/g
normal	-	5	0.1011 ± 0.0149	0.6012 ± 0.0618	335.12 ± 21.75	0.30 ± 0.03	1.79 ± 0.16	0.17 ± 0.02
MCT-treated	60	5	0.1185 ± 0.0250	0.5521 ± 0.0738	311.77 ± 18.47	0.38 # ± 0.07	1.77 ± 0.17	0.22 # ± 0.04

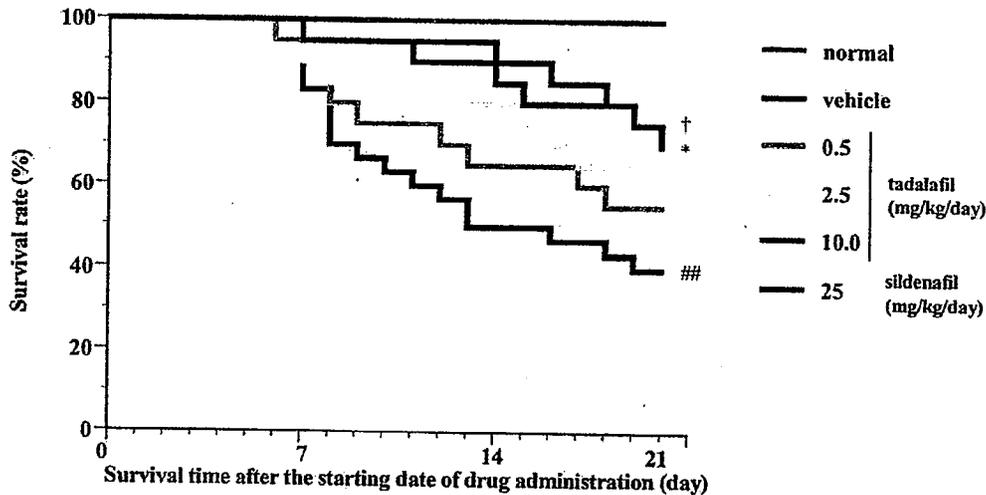
Cardiac weight measurement was performed on Day 21~Day 23 (Day 1 denotes the day of MCT injection).  
Data are shown as mean ± S.D.

MCT-treated group vs normal group; Student's t-test, #: p < 0.05

Definition of abbreviations:

RV = weight of right ventricle; LV+S = weight of left ventricle and septum; BW = body weight;  
RV/BW = ratio of RV to BW; (LV+S)/BW = ratio of LV+S to BW; RV/(LV+S) = ratio of RV to LV+S

In the main study groups, tadalafil (10 mg/kg/day) and sildenafil (25 mg/kg/day) improved survival compared to the vehicle control group.



Survival analysis was performed from Day 21 to Day 41 (Day 1 denotes the day of MCT injection).

Drugs were orally administered from Day 21 to Day 41. Tadalafil was administered once a day, but sildenafil was twice a day.

Survival time shows the survival time after the starting date of tadalafil or sildenafil administration.

Vehicle group vs normal group; Kaplan-Meier Log-Rank test, ##: p < 0.01.

Tadalafil group vs vehicle group; Kaplan-Meier Log-Rank test (multiple comparison), \*: p < 0.05.

Sildenafil group vs vehicle group; Kaplan-Meier Log-Rank test, †: p < 0.05.

Tadalafil and sildenafil increased plasma and lung levels of cGMP in animals that survived for 6 weeks after MCT administration.

Group	Dose mg/kg/day	Number of rats	plasma cGMP pmol/mL	lung cGMP pmol/wg
normal	-	10	4.68 ± 1.75	46 ± 7
vehicle	-	12	8.12 ± 6.53 (9)	62 # ± 18
tadalafil	0.5	11	25.63 ± 21.11 (8)	119 * ± 36
	2.5	12	75.88 ** ± 38.40 (8)	187 ** ± 91
	10.0	14	69.67 ** ± 40.99 (12)	187 ** ± 86
sildenafil	25	15	69.63 †† ± 50.70 (12)	243 †† ± 131

Extraction of plasma or lung tissue was performed on Day 41 (Day 1 denotes the day of MCT injection).

Drugs were orally administered from Day 21 to Day 41. Tadalafil was administered once a day, but sildenafil was twice a day.

Each value in parenthesis is represented as number of rats.

Vehicle group vs normal group; Aspin-Welch's t-test, #:  $p < 0.05$

Tadalafil group vs vehicle group; Dunnett type mean rank test, \*:  $p < 0.05$ , \*\*:  $p < 0.01$

Sildenafil group vs vehicle group; Aspin-Welch's t-test, ††:  $p < 0.01$

Data are shown as mean ± S.D.

Definition of abbreviations:

cGMP = cyclic guanosine 3', 5'-monophosphate; wg = wet weight

Tadalafil did not affect right ventricular weight, in contrast to sildenafil, which lowered right ventricular weight relative to left ventricular weight in those animals that survived for 6 weeks after MCT administration.

Group	Dose mg/kg/day	Number of rats	RV g	LV+S g	BW g	RV/BW g/kg	(LV+S)/BW g/kg	RV/(LV+S) g/g
normal	-	10	0.1080 ± 0.0195	0.7014 ± 0.0937	406.80 ± 39.60	0.27 ± 0.06	1.73 ± 0.21	0.15 ± 0.03
vehicle	-	12	0.2806 ## ± 0.0309	0.5635 ## ± 0.0704	301.41 ## ± 40.46	0.95 ## ± 0.19	1.89 ± 0.28	0.50 ## ± 0.07
tadalafil	0.5	11	0.3159 ± 0.0400	0.5678 ± 0.0685	289.22 ± 45.67	1.11 ± 0.21	1.99 ± 0.28	0.56 ± 0.08
	2.5	12	0.2862 ± 0.0508	0.5757 ± 0.0888	300.94 ± 44.00	0.96 ± 0.20	1.92 ± 0.21	0.51 ± 0.11
	10.0	14	0.2377 ± 0.0759	0.6236 ± 0.1243	290.35 ± 63.58	0.86 ± 0.34	2.18 * ± 0.26	0.40 ± 0.17
sildenafil	25	15	0.2462 ± 0.0547	0.6702 †† ± 0.0856	293.94 ± 37.97	0.86 ± 0.27	2.31 †† ± 0.37	0.37 †† ± 0.09

Cardiac weight measurement was performed on Day 41 (Day 1 denotes the day of MCT injection).

Drugs were orally administered from Day 21 to Day 41. Tadalafil was administered once a day, but sildenafil was twice a day.

Data are shown as mean ± S.D.

Vehicle group vs normal group; Student's t-test (RV, LV+S and BW) or Aspin-Welch's t-test (RV/BW and RV/(LV+S)), ##:  $p < 0.01$

Tadalafil group vs vehicle group; Dunnett's test, \*:  $p < 0.05$

Sildenafil group vs vehicle group; Student's t-test, ††:  $p < 0.01$

Definition of abbreviations:

RV = weight of right ventricle; LV+S = weight of left ventricle and septum; BW = body weight;

RV/BW = ratio of RV to BW; (LV+S)/BW = ratio of LV+S to BW; RV/(LV+S) = ratio of RV to LV+S

### Relationship of PDE5 Inhibition to In Vivo Plasma Concentrations in Pulmonary Hypertensive Patients

The following discussion is an attempt to relate free plasma tadalafil concentrations to PDE5 inhibition.

Tadalafil inhibits PDE5 with an IC<sub>50</sub> of 0.94 nM.<sup>2</sup> Maximum plasma concentrations of tadalafil in healthy Caucasian subjects given single oral doses of 5, 10, 20 or 40 mg are shown (Study LVCS) along with the ratio of free plasma concentration vs the IC<sub>50</sub> for PDE5 inhibition. As shown in the table, maximum free plasma tadalafil concentrations ranged from 16 to 92 times the PDE5 IC<sub>50</sub> following single oral doses of 5 mg to 40 mg. In comparison, the maximum plasma sildenafil concentration in pulmonary hypertensive patients given 20 mg tid, orally is only 1.8 times its IC<sub>50</sub> for PDE5 inhibition.<sup>3</sup> The minimum plasma sildenafil concentration following this dose is only 0.5 times its IC<sub>50</sub> for PDE5 inhibition.

Drug	Oral Dose (mg)	Plasma Drug Levels			C <sub>plasma free</sub> (nM) /IC <sub>50</sub> (nM) ratio
		Total		Free	
		(µg/l)	(nM)	(nM)	
Tadalafil <sup>a</sup>	5	101 (31.4)	259 (80)	15 (4.8)	16
	10	187 (29.0)	481 (74)	29 (4.5)	31
	20	318 (29.9)	817 (77)	49 (4.6)	52
	40	562 (26.6)	1444 (38)	87 (4.1)	92
Sildenafil <sup>b</sup>	20	107 [28]	160 [42]	6.4 [1.7]	1.8 [0.5]
	40	206 [56]	309 [84]	12.3 [3.4]	3.5 [1.0]
	80	503 [146]	754 [219]	30 [8.8]	8.6 [2.5]

a. For tadalafil: Maximum plasma concentration (coefficient of variation, %); Percent protein bound, 94%; molecular wt, 389.41; PDE5 IC<sub>50</sub>, 0.94 nM.

b. For sildenafil: Maximum and [minimum] plasma concentrations and ratios to the PDE5 IC<sub>50</sub>; Percent protein bound, 96%, molecular weight, 666.7; PDE5 IC<sub>50</sub>, 3.5 – 3.9 nM

<sup>2</sup> Overview of Phosphodiesterase 5 Inhibition in Erectile Dysfunction.

Am. J. Cardiology. 2003; 92 (suppl): 9M-18M.

<sup>3</sup> Sildenafil plasma concentrations were taken from Clinical Pharmacology and Biopharmaceutics Review (NDA21845); 5/20/2005, Elena Mishina, Ph.D.

Sponsor's Tables of Nonclinical Study Exposures to Tadalafil and Multiples of Human Exposure

**Table 1 Comparison of Exposure (Based on AUCs) for Unbound Tadalafil in Mouse and Rat Carcinogenicity and Reproduction/Developmental Studies and Human PAH Patients**

USPI Section	Study Cited (study #, report reference)	Study Day NOEL Dose (mg/kg)	Total AUCs (ng*hr/mL)		Unbound AUCs (ng*hr/mL)		Multiple of Human Exposure Unbound <sup>a</sup>	
			Male	Female	Male	Female	Male	Female
13.1 carcinogenesis	Mouse oncogenicity CTBR 88780 (Tox 40)	Day 180 400	31223	20962	4683	3144	♂ <sup>c</sup>	4
13.1 carcinogenesis	Rat oncogenicity CTBR88779 (Tox 38)	Day 180 400	78863	152863	6309	12229	7	14
8.1 teratogenicity	Mouse embryofetal WIL353004 (Tox 7)	Day 11 1000		36752		5513		6
8.1 teratogenicity	Rat embryofetal WIL353005 (Tox 8)	Day 12 1000		80179		6414		7
8.1 postnatal	Rat postnatal WIL353016 (Tox 39)	Day 19 30 <sup>b</sup> 200		55590 91115		4447 7289		5 8
13.1 fertility, rat 13.2 animal tox	6 month rat R21236 (Tox 4)	Day 168 60 <sup>c</sup> 400 <sup>d</sup>	29100 72200	82900 190000	2328 5776	6632 15200	3 6	7 17

...continued

**Table 1 (continued) Comparison of Exposure (Based on AUCss) for Unbound Tadalafil in Mouse and Rat Carcinogenicity and Reproduction/Developmental Studies and Human PAH Patients**

USPI Section	Study Cited (study #, report reference)	Study Day NOEL Dose (mg/kg)	Total AUCss (ng*hr/mL)		Unbound AUCss (ng*hr/mL)		Multiple of Human Exposure Unbound <sup>a</sup>	
			Male	Female	Male	Female	Male	Female
13.2 animal tox	3 month mouse M04298, M04398 (Tox 9)	Day 90						
		60 <sup>e</sup>	7886	13492	1183	2024	<i>1</i>	2
		200	17822	22699	2673	3405	3	4
		400	18559	19827	2784	2974	3	3
		800	20004	22421	3001	3363	3	4

NOEL = no observed effect level

<sup>a</sup> Human AUCss (ng\*h/mL) = 14825.5, Clinical Study LVGY, 40-mg/day dose, steady state). Exposure multiples are corrected for the % unbound tadalafil (that is, 6% in humans, 15% in mice, and 8% in rats). Mouse AUC\*(0.15)/Human AUC\*(0.06); Rat AUC\*(0.08)/Human AUC\*(0.06).

<sup>b</sup> NOEL for postnatal survival = 30 mg/kg; however, decreased postnatal survival was not observed in a second pre-/postnatal developmental study at a dose of 200 mg/kg.

<sup>c</sup> NOAEL dose (no observed adverse effect level)

<sup>d</sup> Exposure values from Tox 4 were used to calculate multiples for fertility study in rats, as the fertility study (Tox report 6) did not include an exposure assessment.

<sup>e</sup> Lymphoid necrosis and hemorrhage occurred at all doses in this study

<sup>f</sup> Exposure multiples in bold and italics are those included in the label

**Table 2 Comparison of Exposure Levels (Based on AUCss) for Unbound Tadalafil in Dog Repeat-Dose Studies and Human PAH Patients**

USPI Section	Study Cited (study #, report reference)	Study Day Dose (mg/kg)	Total AUC0-t (ng*hr/mL)		Unbound AUC0-t (ng*hr/mL)		Multiple of Human Exposure Unbound*	
			AUC Range <sup>b</sup>		AUC Range		Multiple Range	
			Male	Female	Male	Female	Male	Female
13.2 arteritis	1 month dog Study D20863 (Tox 27)	Day 27	8060	3280	1048	426	1.2	0.5 <sup>c</sup>
		10	7090	24300	922	3159	1	4
		45 <sup>c</sup>	220000	135000	28600	17550	32	20
		200						
13.1 fertility, dog and 13.2 arteritis	1 <sup>st</sup> 6th month dog Study D21235 (ISU04C; Tox 20)	Day 182	4350 to 43200	4960 to 26900	566 to 5616	645 to 3497	0.6 to 6.3 <sup>h</sup>	0.7 to 3.9
		10 <sup>d</sup>	68300 to 179000	44300 to 261000	8879 to 23270	5759 to 33930	10 to 26	6 to 38
		400						
13.1 fertility, dog	2 <sup>nd</sup> 6 month dog CTBR88632 (Tox 23)	Day 176	3772 to 6882	4105 to 6202	490 to 895	534 to 806	0.6 to 1.0 <sup>h</sup>	0.6 to 0.9
		10 <sup>e</sup>	31384 to 91270	41786 to 129341	4080 to 11865	5432 to 16814	5 to 13	6 to 19
		400						

...continued

**Table 2 (continued) Comparison of Exposure Levels (Based on AUCss) for Unbound Tadalafil in Dog Repeat-Dose Studies and Human PAH Patients**

USPI Section	Study Cited (study #, report reference)	Study Day Dose (mg/kg)	Total AUC0-t (ng*hr/mL)		Unbound AUC0-t (ng*hr/mL)		Multiple of Human Exposure Unbound <sup>a</sup>	
			AUC Range <sup>b</sup> Male	AUC Range Female	AUC Range Male	AUC Range Female	Multiple Range Male	Multiple Range Female
13.2 cytopenia	One year dog D01899 (Tox 36)	Day 364 <sup>f</sup>	8576 to 43136	8792 to 68012	1115 to 5608	1143 to 8842	1.3 to 6	1.3 to 10
		25						
	Non-cytopenic females	Day 177 100 mg/kg 400 mg/kg	34900 to 93491 51103 to 146404		4537 to 12154 6643 to 19033		5 to 14 7 to 21	
	Cytopenic females	Day 177 100 mg/kg 400 mg/kg	Dog 283863 Dog 284504	71385 28862	9280 3752	10 4		

<sup>a</sup> Human AUCss (ng\*h/mL) = 14825.5, Clinical Study LVGY, 40-mg/day dose, steady state). Exposure multiples are corrected for the % unbound tadalafil (that is, 6% in humans, 13% in dogs. Dog AUC\*(0.13)/Human AUC\*(0.06).

<sup>b</sup> Due to high variability in exposure the exposure multiples are reported as a range from lowest to highest exposure, except for the 1 month study where the reported values are the mean

<sup>c</sup> NOEL (no observed effect level) dose was the mid-dose of 45 mg/kg

<sup>d</sup> NOAEL (no observed adverse effect level) in females = 10 mg/kg but a NOEL/NOAEL was not identified in males

<sup>e</sup> NOAEL for testicular effects = 10 mg/kg, NOAEL in females = 400 mg/kg.

<sup>f</sup> NOAEL for testicular effects in males = <25 mg/kg, NOAEL in females = 25 mg/kg. Cytopenia was observed in 2 of the 4 female dogs. Plasma levels and exposure multiples are shown for the female dogs that exhibited cytopenia and for the remaining female dogs that did not exhibit cytopenia (non-cytopenic).

<sup>g</sup> Exposure multiples in bold and italics are those included in the label

<sup>h</sup> Actual numbers not included in label, referred to as being similar to human exposures at 40 mg

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