CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-368

PHARMACOLOGY REVIEW

GENERAL PHARMACOLOGY/TOXICOLOGY COVER SHEET

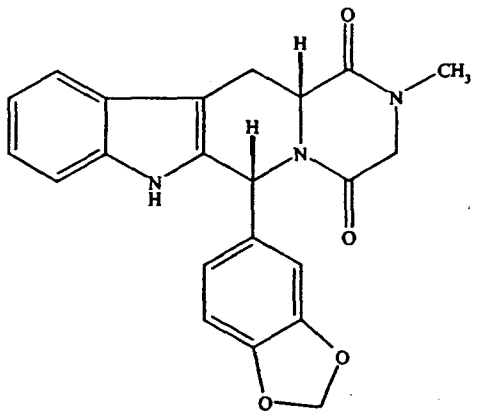
NDA No: 21-368 **Review No:** 1
Sequence No: 000 **Date/type of submission:** June 28, 2001/Original
Information to sponsor: Yes (x) No ()
Sponsor: Lilly ICOS LLC, Eli Lilly & Company, Indianapolis, IN 46285
Manufacturer for drug substance: Eli Lilly & Co., Tippecanoe Laboratories, Lafayette, IN 47909

Reviewer: Yangmee Shin, Ph.D.
Division: Division of Reproductive and Urologic Drug Products, HFD-580
Review completion date:

Drug:

Trade name: Cialis **Generic name:** Tadalafil
Code name: IC351 (LY450190)
Chemical name: Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R-12aR)-

CAS registry No: 171596-29-5 **Mole file No:**
Molecular formula: $C_{22}H_{19}N_3O_4$ **Molecular weight:** 389.41
Structure:



Relevant INDs/NDAs/DMFs: IND 54,553 .
Drug class: β-carboline phosphodiesterase (PDE) type 5 inhibitor
Indication: Erectile Dysfunction (ED)

Clinical formulation: Yellow, 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.

Route of administration: Oral

Proposed clinical use: Treatment of erectile dysfunction

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Studies reviewed within this submission:

PHARMACOLOGY (#S21422, #01-0007-11, #00-0010-11, #00-0009-11)
TOXICOKINETICS (#D01899, # — 88780, # — 88779, # —-353016)
TOXICOLOGY
1-Year oral toxicity study in beagle dogs (vol. 31, p 1, #D01899)
CARCINOGENICITY
2-Year oral carcinogenicity study in CD-1 mice (vol. 33, p 1, # — 88455)
2-Year oral carcinogenicity study in l— Wistar rats (vol. 34, p 1, # — 88203)
REPRODUCTIVE TOXICOLOGY
Segment II & III reproductive study in CD rats (vol. 37/38, p 1, # — -353010 —-353016)

Studies <u>not</u> reviewed within this submission (Appendix I):

<u>IND 54,553 Review #1, May 26, 1998</u>
PHARMACOLOGY (#97-001-14, #97002-14, #97-003-14, # — 94-007)
SAFETY PHARMACOLOGY (#20215, #S20996, #21011, #S20222, #97-004-14)
PHARMACOKINETICS
Absorption (#R21147, #D21148, #BPW662, #BPW641/BPW659)
Metabolism (#BPW549/BPW564, #BPW641/BPW659)
Distribution (#BPW618)
Protein binding (#BPW507, #BPW495)
TOXICOKINETICS (#R20861, #R21236, #D21148, #D20786, #D20863, #D21235)
TOXICOLOGY
Acute toxicity (#M20798, #M20799, #M20977, #M20978, #R20796, #R20797, #R20979, #R20980)
Repeated toxicity
1. Maximum repeatable daily oral dosage study in the — Wistar Rat (#R20791)
2. 1-Month oral toxicity study in — Wistar Rats (#R20861)
3. Study to determine the maximum repeatable daily oral dosage in the beagle dog (#D20786)
4. 1-Month oral toxicity study in the beagle dog (#D20863)
5. 6-Month oral toxicity study in the beagle dog (#D21235)

GENETIC TOXICOLOGY
1. Microbial mutagenicity study (#U20206)
2. Mouse lymphoma thymidine kinase mammalian cell mutation study (#V21166)
3. *In vitro* cytogenetic evaluation in cultured human lymphocytes (#V20918)
4. WHO nitrosation assay (#U21004)

<u>IND 54,553 Review #2</u>
TOXICOLOGY
1. 6-Month oral toxicity study in the beagle dog (#D21235)

<u>IND — Review #1, May 27, 1999</u>
PHARMACOKINETICS
Metabolism (#1999IV-RSL05, #006R00)
Excretion (#BPW549/BPW564)
TOXICOKINETICS (#88270)
TOXICOLOGY
1. 3-Month oral pilling toxicity study with a 13-week recovery period in the Beagle dog (#88270)

GENETIC TOXICOLOGY
1. Micronucleus assay in bone marrow of male — Wistar Rats (#R20937)

<u>IND — Review #2, Jul 26, 1999</u>
SAFETY PHARMACOLOGY (#PG9927)
TOXICOKINETICS (#M04298, #R18498, #M04398, # — 353004, # — -353005)
TOXICOLOGY
1. 1- & 3-Month oral gavage toxicity in CD-1 mice (#M04298)

REPRODUCTIVE TOXICOLOGY
1. Embryo/fetal development in CD-1 mice (# —353004)
2. Embryo/fetal development in CD rats (# —353005)

IND 54,553 Review #3, Aug 10, 1999
PHARMACOLOGY (#98-0001-11, #98-0002-11, #98-0003-11)
PHARMACOKINETICS (#132R98, #R14998, #M04198, ADME#6, ADME#7)
TOXICOKINETICS (# 88440, #21236)
TOXICOLOGY
1. 3-Month oral gavage toxicity in CD-1 mice (#88437)
2. 6-Month oral gavage toxicity in Wistar rats (#21236)

REPRODUCTIVE TOXICOLOGY
1. Oral gavage fertility study in CD rats (#96364)

JUSTIFICATION FOR 2-YEAR CARCINOGENICITY STUDY DOSE SELECTIONS IN RATS & MICE

IND — Review #3, Sep 3, 1999
PHARMACOLOGY (#PR9902)
PHARMACOKINETICS (#B00199, #R18498)
TOXICOKINETICS (#R18498, 88632)
TOXICOLOGY
1. 3-Month oral gavage in Fisher 344 rats (#R18498)
2. 6-Month oral pilling toxicity study with a 3-month recovery period in the Beagle dog (88632)

SPECIAL TOXICOLOGY
1. *In vitro* ocular irritation-agar diffusion cytolysis & aqueous pH in cultured rabbit cornea cells (#990416ADC)

IND — Review #4, Dec 27, 1999
PHARMACOLOGY (#PR9902)
SPECIAL TOXICOLOGY
1. *In vivo* eye irritation study in New Zealand White rabbits (#SLI3130.495)
2. *In vivo* acute dermal toxicity in New Zealand White rabbits (#SLI3130.487)

IND — Review #5, Aug 15, 2000
PHARMACOLOGY (#1999IV-EI004, #PR9906, #99-0005-11)
PHARMACOKINETICS
Distribution (#003R00)
Metabolism (#1999IV-SF038)
Excretion (#078R99, #002R00)
Repeat Dose in Monkeys (88548)

Introduction and drug history: IC351 is a potent, competitive and reversible inhibitor of cGMP specific PDE type 5 for an indication of ED under IND 54,553. It is also currently being investigated for — under IND — Major toxicities are irreversible seminiferous testicular atrophy and vasculitis in dogs. The original submission by ICOS Corporation was placed on clinical hold because of vasculitis findings in dogs and the high daily clinical dose up to 100 mg.

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on Approvability: The preclinical studies conducted support the safety of the proposed dose of 20 mg of Cialis.

B. Recommendation for Nonclinical Studies: The 2-year carcinogenicity studies in male rats, and male and female mice were conducted at doses below those recommended by the ICH guidelines (see Exectutive CAC minutes in appendex II) based on the AUC exposures for the 20 mg human dose. The Committee recommended an additional alternative mouse carcinogenicity assay be conducted for Phase IV commitment unless the sponsor provided evidence for saturation of absorption by measuring either total radioactivity or metabolites.

C. Recommendations on Labeling: Refer to the labeling comments.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings: Effective antihypertensive oral doses of IC351 were 1 mg/kg in the rat. Reduction in mean blood pressure occurred at doses from 20 mg/kg without effects on heart/respiration rate in conscious dogs, but moderate tachycardia was seen in a dog (1/2) at 30 mg/kg and in both dogs at 100 mg/kg in another study. The cardiovascular effects were not observed in the repeated toxicity studies. IC351 potentiated atrial natriuretic factor (ANF)-induced diuresis and natriuresis in rats at lower doses (0.1 mg/kg, i.v.) than those required for decreasing blood pressure. Slight-to-moderate ptosis and depression of the pinnal reflex were observed in rats given 200 mg/kg. IC351 did not cause death up to 2,000 mg/kg (p.o.) in mice and rats in acute studies. Like other PDE5 inhibitors, the major findings of IC351 treatment in repeated dose studies are arteritis and testicular degeneration/atrophy observed in multiple species. IC351 was not genotoxic and the carcinogenicity studies were negative although hepatocellular adenomas/carcinomas were observed with increased frequency in high dose male mice and rats. Reproductive and developmental studies in mice and rats displayed no adverse effects on fertility at doses up to 1,000 mg/kg. Mice were used for a second rodent species of embryo/fetal development studies since plasma exposure for rabbits was minimal. A NOAEL for maternal toxicity was established at 1,000 mg/kg in mice and 200 mg/kg in rats (based on reduced body weight gain). A NOAEL for F1 developmental toxicity in the rat could not be identified due to significantly reduced postnatal survival in all dose groups from the combined segment II/III study. Sponsor defined a NOAEL of 30 mg/kg from a subsequent study, which gives 9-fold exposure for the unbound parent drug (pregnant rat) to the human exposure at 20 mg. IC351 is a mild ocular and dermal irritant in New Zealand White rabbits.

B. Pharmacologic Activity: IC351 is a potent and selective inhibitor of PDE5 among the PDEs tested *in vitro*. PDE5 is a major cGMP-hydrolyzing enzyme in human cavernosal smooth muscle, and the inhibition of PDE5 by IC351 enhances relaxant effects of NO by stimulating cGMP levels. This leads to relaxation of penile resistance arteries and the smooth muscle to enhance the erectile response. IC351 strongly potentiated the inhibitory effects of sodium nitroprusside (SNP) on human platelet aggregation with complete inhibition at 0.25 μM, and on increased cGMP levels in human cavernosal smooth muscle, suggesting that the PDE5 inhibition by IC351 may lead to large increases in cGMP levels once activated. IC351 retains relatively low selectivity for PDE5 vs. human PDE11A (abstract from Am. Coll. Clin. Pharmacol., VA, 2001), which was widely expressed in kidney, liver, pituitary/salivary glands and testis (PNAS **97:** 3702, 2000). Thus, pharmacological characterization of IC351 on human PDE11A may provide additional information on the mechanism of IC351.

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