CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-863

PHARMACOLOGY REVIEW(S)

BUEHLER

NDA 20,863

REVIEW AND EVALUATION OF PRECLINICAL PHARMACODYNAMIC AND PHARMACOKINETIC DATA

John E. Koerner, Ph.D.

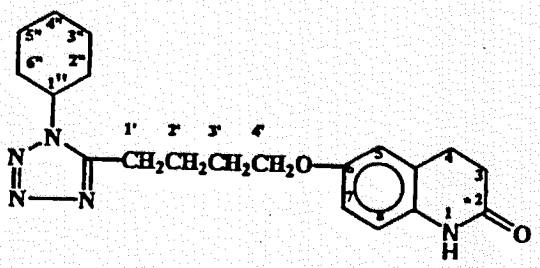
SUBMISSION DATE: 09/18/97
CENTER RECEIPT DATE: 09/22/97
REVIEWER ASSIGNMENT DATE: 09/23/97

AUG - 6 1998

SPONSOR: Otsuka America Pharmaceutical, Inc.

DRUG PRODUCT: Pletal Tablets

DRUG: Generic Name: Cilostazol
Code Name: OPC-13013
Chemical Name: 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxyl]-3-4-dihydro 2(1H)-quinolinone
Chemical Structure:



Molecular Weight: 369.47

FORMULATION AND ROUTE OF ADMINISTRATION: Tablets for oral administration containing either 50 or 100 mg of cilostazol, along with corn starch, micro-crystalline cellulose, carboxymethylcellulose calcium, hydroxypropyl methylcellulose, and magnesium stearate.

PHARMACOLOGICAL CLASS: Phosphodiesterase III Inhibitor:

PROPOSED INDICATION: Intermittant Claudication

PROPOSED DOSAGE REGIMEN: 50 or 100 mg, bid

IND UNDER WHICH CLINICAL TRIALS WERE CONDUCTED:

BACKGROUND

The sponsor submitted reports of 178 pharmacodynamic studies in this NDA submission. This review discusses studies relative to purported mechanisms of action; i.e., phosphodiesterase inhibition, platelet antiaggregatory effects, and vascular relaxant effects. Cardiac effects of cilostazol in animal models will also be discussed, as these effects relate to cilostazol's preclinical safety profile. Finally, pharmacodynamic effects of two major human metabolites will be discussed. The sponsor's Comprehensive Review of the Non-Clinical Pharmacology of Cilostazol (OPC-13013), as annotated by the reviewer, provides summaries of these and other studies (see attachment).

The sponsor also submitted reports of 90 preclinical pharmacokinetic studies. The sponsor's Comprehensive Review of Absorption, Distribution, Metabolism and Excretion (ADME) of Cilostazol, as annotated by the reviewer, provides summaries of those and other studies (see attachment).

OVERALL SUMMARY AND EVALUATION OF PHARMACODYNAMICS

Cilostazol selectively inhibited phosphodiesterase III (PDE III) isolated from platelets, vascular smooth muscle, and myocardium, with inhibitory concentrations (IC_{50}s) of 0.19, 0.44 and 0.46 μM, respectively. PDE III is a cyclic GMP- inhibitable phosphodiesterase that hydrolyzes cyclic AMP.

Consistent with inhibition of PDE III, cilostazol increased cyclic AMP levels in human platelets at 30 and 100 μM, in rabbit platelets at 3-100 μM (in the presence of PGE_1), in canine femoral artery at 10 μM (in the presence of forskolin), and in cultured rat aortic smooth muscle cells at 1-30 μM. Activation of adenylate cyclase with PGE_1 (rabbit platelets) and forskolin (canine femoral artery) increased the sensitivity of these tissues to the cAMP increasing effects of cilostazol. Cilostazol also inhibited thrombin-induced calcium mobilization in human platelets at 10 and 100 μM, consistent with cilostazol-induced cyclic AMP increases.

Several pharmacological effects were demonstrated with cilostazol that are consistent with inhibition of PDE III. Cilostazol was shown to inhibit platelet aggregation *in vitro*, using platelets from mice, rats, dogs, rabbits and humans. In human platelets, the inhibitory concentrations (IC_{50}s) of cilostazol ranged from and were dependent on the agent utilized to induce platelet aggregation (ADP, collagen, epinephrine and arachidonic acid). Consistent with PDE III inhibition, the dose response relationship for cilostazol's increase in cyclic AMP in human platelets paralleled its platelet antiaggregatory effect. Additionally, the potency for the antiplatelet aggregatory effect of cilostazol for shear stress-induced aggregation of human platelets was increased in the presence of PGE_1, similar to the interaction of cilostazol with PGE_1 seen for cyclic AMP increases.

Oral administration of cilostazol inhibited platelet aggregation, *ex vivo*, in mice at 300 mg/kg, in

female rats at 10 and 30 mg/kg, and in dogs at 10 and 30 mg/kg. Cilostazol's platelet antiaggregatory effects were evident both with a single oral dose and with repeat oral doses in female rats at 100 mg/kg for 2 weeks, and in dogs at 10 and 30 mg/kg for 8 days, indicating that tachyphylaxis did not occur. *In vivo*, intraduodenal administration of cilostazol at 300 mg/kg inhibited cyclic flow reductions in stenosed coronary arteries of anesthetized dogs with damaged endothelium. Cyclic flow reductions (CFRs) in this canine model are due to spontaneous formation of platelet-mediated thrombi, which occlude the coronary artery, followed by dislodgement of the platelet thrombi, with resumption of coronary blood flow. CFRs are responsive to platelet active agents such as aspirin, and serotonin (5HT2) receptor antagonists (ketanserin, ritanserin).

Also consistent with cilostazol's PDE III inhibition was vascular relaxation induced with this agent. *In vitro*, cilostazol relaxed several isolated canine arteries (femoral, middle cerebral, basilar, vertebral and internal carotid) and femoral veins that were precontracted with a variety of contractile agents (KCl, $PGF_{2\alpha}$, or norepinephrine). Cilostazol concentrations (EC_{50}s) that were effective in relaxing canine femoral arterial preparations ranged from approximately Vascular relaxant potencies for cilostazol in different arteries of the dog were compared; the *in vitro* vascular relaxant potency of cilostazol was in the order of femoral>middle cerebral>basilar arteries. Cilostazol also relaxed human subcutaneous resistance arteries *in vitro*; the EC_{50} for vascular relaxation of human vessels was approximately 3.0 μM. The potencies for cilostazol's *in vitro* vascular relaxation effects were independent of the presence or absence of an intact vascular endothelium (canine femoral, vertebral, and internal carotid arteries, and human subcutaneous resistance arteries), indicating that the endothelium was neither necessary nor important for cilostazol's vasorelaxant activity.

In vivo, intra-arterial administration of cilostazol to anesthetized dogs at doses of 1-100 μg increased blood flow in several arteries that were perfused at constant pressure from an extracorporeal circuit. In these experiments, canine arteries exhibited a differential sensitivity to cilostazol, similar to the findings *in vitro*. The *in vivo* sensitivities of canine arteries to cilostazol were in the order of femoral >vertebral>internal carotid>superior mesenteric arteries. Renal arteries were insensitive to cilostazol at doses sufficient to increase blood flow in other vascular beds. It should also be noted that the *in vivo* vascular relaxant effects of cilostazol in canine arteries were not affected by prior blockade of β-adrenergic receptors with propranolol, indicating that vascular relaxation was not dependent on β-adrenergic receptor agonism.

Several cardiac and hemodynamic effects were observed with cilostazol *in vitro* and *in vivo* at doses similar to those necessary for vascular relaxant effects. Intraarterial administration of 1-100 μg cilostazol into coronary arteries of isolated, blood perfused canine hearts increased myocardial contractile force, sinus rate, and ventricular automaticity, and accelerated conduction through the AV node, while increasing coronary blood flow in these preparations. Intravenous administration of 0.1-1.0 mg cilostazol/kg to anesthetized dogs decreased diastolic blood pressure, and increased heart rate, myocardial contractile force, coronary blood flow, and myocardial oxygen consumption; these doses also increased blood flow in femoral, internal

carotid, and vertebral arteries. In conscious dogs, intravenous administration of cilostazol at 0.3 and 1.0 mg/kg increased left ventricular +dP/dt max, an index of cardiac contractility, without significantly affecting heart rate, arterial blood pressure, or cardiac output. In anesthetized cynomolgus monkeys, intravenous cilostazol administration increased heart rate, and left ventricular +dP/dt max, and decreased mean blood pressure at similar doses (ED_{10}, heart rate, 0.5 mg/kg; ED_{25}, LV +dP/dt, 0.15 mg/kg; ED_{20}, mean blood pressure, 0.44 mg/kg). The sponsor calculated that cilostazol increased heart rate by 4-6% at a dose that increased left ventricular +dP/dt by 25%. A similar pattern was noted in cynomolgus monkeys given the PDE III inhibitor, amrinone.

Oral administration of cilostazol to conscious dogs at doses of 10, 30 and 100 mg/kg increased left ventricular +dP/dt max. The magnitude (50-60% over vehicle control) of the increase was similar at all three doses. The duration of the increase in left ventricular +dP/dt max was also unrelated to dose; left ventricular +dP/dt was increased for at least 6-8 hours but less than 24 hours at all doses evaluated. Oral administration of cilostazol at 100 mg/kg tended to increase heart rate, while mean arterial blood pressure was not affected by any dose of cilostazol. In this study, plasma cilostazol concentrations were dose related, as were plasma concentrations of OPC 13015 and OPC 13213, the two major human metabolites. Several other studies with oral cilostazol administration in conscious dogs confirmed the finding of an increase in left ventricular +dP/dt max.

Several metabolites of cilostazol were determined to be potent inhibitors of cAMP-phosphodiesterase isolated from human platelets, and inhibitors of platelet aggregation induced by ADP and collagen. PDE III is the major cAMP-phosphodiesterase found in human platelets. The major metabolites found in human plasma, OPC 13015 and OPC 13213, were shown to be approximately 7 (seven) and 0.2 times, respectively, as potent as cilostazol as cAMP-phosphodiesterase inhibitors. Similar potency differences were observed for these agents' platelet antiaggregatory effects. OPC 13015 also increased blood flow when administered into canine femoral arteries, with a potency similar to that of cilostazol.

In a recent amendment to the NDA (dated July 2, 1998), the sponsor provided reports of three *in vitro* assays comparing effects of cilostazol and milrinone at concentrations of 1-100 μM on 1) cardiac contractility (+LV dP/dt_{max}) in isolated, perfused rabbit hearts (preliminary report; only percent changes provided, and full dose response relationships and time courses for effects were not evaluated), 2) cAMP concentrations in human platelets and rabbit ventricular myocytes, and 3) adenosine uptake in human coronary artery smooth muscle and endothelial cells. In these studies, cilostazol was less potent than milrinone at increasing cardiac contractility in isolated rabbit hearts, and increasing cAMP levels in rabbit ventricular myocytes. Cilostazol and milrinone were similarly potent at increasing cAMP levels in human platelets. Cilostazol, but not milrinone, decreased adenosine uptake by human vascular smooth muscle and endothelial cells. While these studies suggest differences between cilostazol and milrinone, they cannot negate positive inotropic effects observed with cilostazol *in vivo* in dogs at doses required for antiplatelet aggregatory effects.

In summary, cilostazol was shown to be an inhibitor of phosphodiesterase III that is present in platelets, vascular smooth muscle and cardiac tissue, an activity which results in an increase in cyclic AMP levels in those tissues. The major human metabolites of cilostazol found in plasma, OPC-13015 and OPC-13213, were also shown to inhibit cAMP-phosphodiesterase. Moreover, the pharmacodynamic effects of cilostazol and its metabolites, including vascular relaxation, inhibition of platelet aggregation, and positive inotropic, chronotropic, and dromotropic activity, can be accounted for by PDE III inhibition. There did not appear to be a separation between doses that induced vascular relaxation or inhibited platelet aggregation and doses that increased heart rate and cardiac contractility.

The PDE III inhibitory effects of cilostazol and its metabolites are of concern, in part due to potential proarrhythmic actions, but primarily due to the negative impact on mortality seen with PDE III inhibitors in congestive heart failure patients. Although there were no specific studies evaluating proarrhythmic potential of this drug, cilostazol was shown to increase ventricular automaticity in canine hearts at doses that increased coronary blood flow, sinus rate, and cardiac contractility.

OVERALL SUMMARY AND EVALUATION OF PRECLINICAL ADME

Oral administration of cilostazol resulted in dose-related exposures to cilostazol (AUCs and Cmax) in male mice, rats, rabbits, dogs, monkeys and humans (Table 5.3-10, pg 58 of sponsor's ADME summary). Absolute bioavailability, volume of distribution, and clearance were not determined. Elimination half lives ranged in rabbits; in comparison, elimination half lives for plasma cilostazol ranged in humans. AUCs were not monitored with repeated daily dosing in dogs or rats. However, accumulation of drug did not appear to occur in male dogs given ^{14}C-cilostazol at 30 mg/kg/day for 7 days, since blood levels of radioactivity at 24 hours after dosing did not change with repeated daily doses (figure 5.3-6, pg 20 of sponsor's ADME summary). In contrast, accumulation of drug appeared to occur in male rats given ^{14}C-cilostazol at 3 mg/kg/day for 21 days, since blood radioactivity levels at 24 hours after dosing increased during this time period (Figure 5.3-5, pg 16 of sponsor's ADME summary).

Exposures to cilostazol and cilostazol-related radioactivity with oral administration were gender related in rats, but not in mice or dogs. Exposures (blood concentrations and AUCs of cilostazol-related radioactivity) in female rats given ^{14}C-cilostazol orally at 3 or 10 mg/kg were significantly greater than exposures in male rats given the same doses. Elimination half lives of cilostazol-related radioactivity were also greater in female than in male rats at 3 and 10 mg/kg, suggesting that clearance was lower in female than in male rats. Plasma concentrations (C_{max}) and AUCs for cilostazol were also higher in female rats than in male rats given unlabeled cilostazol orally at 6, 30, 150 or 1500 mg/kg/day by gavage for 4 weeks (Table 5.3-11, pg 59 of sponsor's ADME summary). Finally, tissue levels of cilostazol-related radioactivity were greater in female than in male rats given a single oral dose of ^{14}C-cilostazol at 3 mg/kg (Section 5.3.5.1., pgs 27-28

of sponsor's ADME summary). In contrast to the gender differences seen in rats, plasma cilostazol concentrations and AUCs were similar in male and female mice given cilostazol orally by diet at 100, 300 and 1000 mg/kg/day for 4 weeks (Table 5.3-11, pg 59 of sponsor's ADME summary). Plasma cilostazol concentrations were also similar in fasted male and female dogs given cilostazol orally at 3 mg/kg (Section 5.3.3.5, pg 19 of sponsor's ADME summary).

In vitro plasma protein binding of cilostazol was evaluated in plasma from rats, dogs, and humans (Table 5.3-3, pg 25 of sponsor's ADME summary). At a cilostazol concentration of 1 μg/ml, plasma protein binding of cilostazol was 99.3%, 93.2, and 96.7% in rat, dog, and human plasma, respectively. Cilostazol binding to human serum albumin was 52.5% at a cilostazol concentration of 1 μg/ml, indicating that a large fraction of protein binding in human plasma could be accounted for by binding to serum albumin. Plasma protein binding of cilostazol metabolites OPC 13015, OPC 13217, and OPC 13213 at a concentration of 1 μg/ml in rat plasma was 87%, 73% and 85%, respectively. Plasma protein binding of cilostazol or its metabolites was not determined for mice or rabbits.

Tissue distribution of drug related radioactivity was evaluated in rats given ^{14}C-cilostazol orally at 3 mg/kg (Table 5.3-4, pg 29 of sponsor's ADME summary). In male and female rats, tissue radioactivity was widely distributed, with high levels seen in liver, stomach and kidneys. Blood levels were approximately 60% of those seen in plasma, indicating that cilostazol related radioactivity was excluded from the erythrocytes. Tissue radioactivity was cleared by 24 hours after cilostazol administration in male rats. The distribution pattern was similar in male and female rats; however, tissue levels in female rats were considerably higher than those in males, consistent with the greater plasma exposure in female than in male rats. Tissue levels in male rats given 3 mg/kg orally for 21 days were slightly higher, and elimination from tissues was slower with multiple doses than with a single dose (Table 5.3-6 of sponsor's ADME summary).

Tissue distribution for pregnant female rats given ^{14}C-cilostazol orally at 3 mg/kg was similar to that seen in nonpregnant female rats given the same dose. Drug related radioactivity (2-6% of plasma radioactivity) was found in the fetus, indicating that the fetus was exposed to cilostazol or its metabolites. Drug related radioactivity was observed in the milk of lactating rats given ^{14}C-cilostazol orally.

Metabolism of cilostazol was studied utilizing microsomes from cells expressing human recombinant cytochrome P450 isoforms. The primary cytochrome P450 isoform shown to be involved in the metabolism of cilostazol was CYP3A4. Cilostazol was also shown to inhibit several human recombinant CYP isoforms: CYP3A4: Ki, 6.4 μM; CYP2C9: Ki, 72 μM; and CYP2C19: Ki, 306 μM. In human liver slices, cilostazol competitively inhibited the metabolism of probe drugs for CYP2C9 (tolbutamide) and CYP2C19 (S-mephenytoin) with Ki's of 85 μM and 44 μM, respectively, but did not inhibit metabolism of the probe drug for CYP3A4 (dextromethorphan) at cilostazol concentrations up to 100 μM.

Cilostazol metabolism by isolated rat liver microsomes was gender related; metabolic rate was

lower in females than in males. This finding is consistent with the greater exposures to cilostazol in female than in male rats with oral administration of cilostazol.

Cilostazol was extensively metabolized in rats, dogs, and rabbits. Metabolite patterns were identified for male mice, rats, dogs, and monkeys (Table 5.3-12, pg 60 of sponsor's ADME summary). The major human metabolites, OPC 13015 and OPC 13213 were identified in plasma from the above-mentioned species. A gender difference in metabolite pattern was noted in rats. While OPC 13015 levels were similar in male and female rats, OPC 13213 levels were considerably lower in female than in male rats (pgs 44-47 of sponsor's ADME summary). The metabolite pattern for female rabbits was not determined; however, in male rabbits given cilostazol orally at 10 mg/kg, the plasma level of OPC 13015 was below the limit of detection.

Elimination routes of cilostazol related radioactivity with single oral dose administration of ^{14}C-cilostazol are shown in Table 5.3-9 for rats given 3 or 10 mg/kg, rabbits given 10 mg/kg and dogs given 3, 12, 30 or 150 mg/kg. To put these doses in context, it should be noted that exposures to cilostazol (Cmax and AUC) in rats and rabbits at the doses given, and in dogs at 3 mg/kg, are considerably lower than exposure in humans given single 50 or 100 mg doses (the human therapeutic doses are 50 and 100 mg, bid). Exposure to cilostazol (Cmax and AUC) in dogs given single oral doses of 30 mg/kg is similar to that in humans given single oral doses of 50 mg. Pharmacodynamic activity (platelet antiaggregatory effect) has been demonstrated in rats and dogs given single oral doses of 10 mg/kg.

Table 5.3-9 shows that at the doses given, most of the drug related radioactivity was excreted in the urine and feces within 24 hours in the male rat and dog, within 48 hours in the nonpregnant and pregnant female rat, and within 72 hours in the male rabbit. In male rats, approximately 40-50% of the drug related radioactivity was eliminated in the urine; in female rats approximately 30-50% of the drug related radioactivity was eliminated in the urine; the remainder was eliminated in the feces for both genders. In male dogs, urinary excretion ranged from 5% to 20% of dose administered. Urinary excretion was inversely related to dose in rats and dogs. In male rabbits, approximately 60% of drug related radioactivity was eliminated by the urinary route. Excretion rates in male rats given 3 mg/kg/day orally for 21 days and dogs given 30 mg/kg/day orally for 7 days were similar to those seen with single doses. Biliary excretion accounted for the majority of fecal excretion in male rats given 3 mg/kg of ^{14}C-cilostazol orally as a single dose. Unchanged cilostazol was not found in the bile or urine of male rats given 10 mg/kg of cilostazol orally.

LABELING RECOMMENDATIONS

The following changes are recommended to the sponsor's proposed package insert (Annotated Labeling, Vol 1, pgs 141-167) provided in the original NDA submission.

Under CLINICAL PHARMACOLOGY, Mechanism of Action, change the following statement (lines 51-60),

THIS PAGE
WAS
DETERMINED
NOT
TO BE
RELEASABLE

John E. Koerner

John E. Koerner, Ph.D.
Pharmacologist
08/05/98

CC:
Original NDA
HFD-110
HFD-110/CSO
HFD-110/Joseph
HFD-110/Koerner
HFD-345
Accepted by EAR on 8-6-98

File: d:\myfiles\NDA20863\reviews\pd20863c.wpd

G Buehler

NDA 20,863

SEP - 3 1998

REVIEW AND EVALUATION OF PRECLINICAL PHARMACOKINETIC DATA

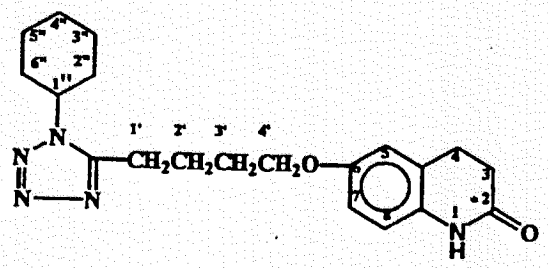
John E. Koerner, Ph.D.

AMENDMENT DATE: 08/19/98
CENTER RECEIPT DATE: 08/19/98
REVIEWER RECEIPT DATE: 08/24/98

SPONSOR: Otsuka America Pharmaceutical, Inc.

DRUG PRODUCT: Pletal Tablets

DRUG: Generic Name: Cilostazol
Code Name: OPC-13013
Chemical Name: 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxyl]-3-4-dihydro 2(1H)-quinolinone
Chemical Structure:



Molecular Weight: 369.47

FORMULATION AND ROUTE OF ADMINISTRATION: Tablets for oral administration containing either 50 or 100 mg of cilostazol, along with corn starch, micro-crystalline cellulose, carboxymethylcellulose calcium, hydroxypropyl methylcellulose, and magnesium stearate.

PHARMACOLOGICAL CLASS: Phosphodiesterase III Inhibitor:

PROPOSED INDICATION: Intermittant Claudication

PROPOSED DOSAGE REGIMEN: 50 or 100 mg, bid

IND UNDER WHICH CLINICAL TRIALS WERE CONDUCTED:

BACKGROUND: Data in the present amendment was provided at the request of this reviewer.

REVIEW OF PHARMACOKINETIC DATA

Determination of Plasma Exposures to Cilostazol and its Major Human Metabolites in Non-Pregnant Female Japanese White Rabbits

Study No.: 014860
Study dates: not provided.

The sponsor provided summary data regarding plasma AUCs for cilostazol and its metabolites (particularly OPC 13015 and OPC 13213) for female rabbits given oral doses utilized in the rabbit developmental toxicity study.

Cilostazol was orally administered at doses of 30, 150 and 1000 mg/kg/day to non-pregnant Japanese female rabbits (16 weeks old) for 13 days. Plasma levels of cilostazol and its major human metabolites were measured on days 1 and 13. The data was internally audited by the sponsor, but details of the study were not provided. Plasma $AUCs_{0\text{-}24hr}$ (ng.hr/ml) for OPC 13013 (cilostazol), OPC 13015 and OPC 13213 are shown below.

The data reveal OPC 13213 to be a major metabolite and OPC 13015 to be a very minor metabolite in the non-pregnant rabbit. Assuming similar pharmacokinetics in pregnant and nonpregnant rabbits, the lowest dose employed in the rabbit developmental toxicity study would be expected to produce systemic exposure to OPC 13015 below the limit of detection.

Day	Compound	$AUC_{0\text{-}24\ hr}$ (ng.hr/ml)		
		30 mg/kg/day	150 mg/kg/day	1000 mg/kg/day
1	OPC 13013	88±89 (3)	630±611 (3)	4201±2691 (3)
	OPC 13213	535±88 (3)	4521±1511 (3)	14200±1513 (3)
	OPC 13015	ND	ND	165±286 (3)
13	OPC 13013	ND	1275±473 (3)	2463±1696 (3)
	OPC 13213	1288±240 (3)	5983±1549 (3)	11563±739 (3)
	OPC 13015	ND	15±25 (3)	47±82 (3)

Mean ± SD
Not determined, below the limit of detection

Determination of *In Vitro* Plasma Protein Binding in Rabbits and Mice

Study No.: not provided
Study dates: not provided

The sponsor provided *in vitro* plasma protein binding data for cilostazol for female rabbits at concentrations encountered under conditions in the rabbit developmental toxicity study, and for male and female B6C3F1 mice at concentrations encountered under the conditions of the mouse carcinogenicity study.

In vitro plasma protein binding of OPC 13013 was 93.8±0.4% at a concentration of 1 μg/ml in female rabbits. *In vitro* plasma protein binding of OPC 13013 was 95.5±0.4% and 96.0±0.5%, in male and female B6C3F1 mice, respectively, at a concentration of 1 μg/ml. In both rabbits and mice, *in vitro* plasma protein binding at an OPC 13013 concentration of 0.2 μg/ml was similar to that at 1.0 μg/ml.

EVALUATION

Exposures to unbound cilostazol at doses used in the two year rat and mouse carcinogenicity studies and the rabbit developmental toxicity study are less than the human exposure to unbound cilostazol at the maximum recommended human dose of 100 mg, bid.

Study	Species	Sex	Dose (mg/kg/day)	Administration	Dose Multiple (mg/M^2)*	AUC_{0-24} Multiple (Unbound Cilostazol)**	Plasma Protein Binding # (%)
Carcinogenicity	Mouse	M	1000	Diet	25	0.82^	95.5
		F	1000	Diet	25	0.57^	96.0
	Rat	M	500	Diet	25	0.11^	99.3
		F	500	Diet	25	0.49@	-
Developmental Toxicity	Rabbit	F	30	Gavage	3	≤0.005^^	93.8
			150		15	0.09^^	
			1000		90	0.17^^	

*Dose multiples are based on the maximum recommended human dose of 100 mg, bid, after surface area correction.
**AUC multiples are based on exposure to unbound cilostazol seen in humans at the maximum recommended human dose of 100 mg, bid, for 8 days; i.e., human $AUC_{0\text{-}24\ hr}$ unbound = 0.042 X 21,600 ng.hr/ml = 907 ng.hr/ml (NDA Vol 42, pg 083, Study Report 21-90-201F).
In vitro plasma protein binding for cilostazol for humans is 95.8% (Dr. R. Uphoor's review of Clinical Pharmacology and Biopharmaceutics, pg 70).
^ Based on AUC data from 4 week dietary administration toxicokinetic studies (Dr. X. Joseph's Review and Evaluation of Toxicology Data, pgs 12 and 14).
^^ Based on AUC data (day 13) from oral toxicokinetic study in non-pregnant female Japanese white rabbits.
@ Plasma protein binding for male rats was used to calculate unbound cilostazol levels in female rats.

LABELING RECOMMENDATIONS

The following changes are recommended for the sponsor's proposed package insert, as revised on August 11, 1998.

Under **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility,**

after the statement, *"The maximum doses administered in both rat and mouse studies are, on a mg/m² basis, about 25 times the maximum recommended human dose (MRHD) of the drug."* , the following should be added:

Under **PRECAUTIONS, Pregnancy,**

after the statement, *" In a rabbit developmental toxicity study, an increased incidence of retardation of ossification of the sternum was seen at doses as low as 30 mg/kg/day (3 times the MRHD)."*, the following should be added:

John E Koerner

John E. Koerner, Ph.D.
Pharmacologist
09/03/98

Attachment: Pages 17, 18 of sponsor's proposed package insert of August 11, 1998.

CC:
Original NDA
HFD-110
HFD-110/CSO
HFD-110/Joseph
HFD-110/Koerner
HFD-345
Accepted by CAL on 9-3-98