CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-863

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

G-Buehler

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20,863 **Submission Date:** September 18, 1997
submitted on 05/27/97

Drug Name and Formulation: Pletal® (Cilostazol) tablets, 50 and 100 mg strengths

Sponsor: Otsuka America Pharmaceuticals, Inc., Rockville, MD 20850

Reviewer: Venkata Ramana S. Uppoor, Ph.D.

Type of Submission: New Drug Application, NME, 1S

SYNOPSIS:

Pletal tablets contain cilostazol, a platelet aggregation inhibitor and vasodilator, in a dosage strength of 50 and 100 mg. This is indicated for the amelioration of symptoms in patients with intermittent claudication. Another drug, pentoxifylline has been previously approved for this indication. Cilostazol is a phosphodiesterase type III inhibitor which prevents platelet aggregation through inhibition of cyclic AMP phosphodiesterase and enhances the effects of PGI_2, the endogenous vessel wall prostaglandin that causes vasodilation. Cilostazol improves the flow of blood to the extremities in patients having intermittent claudication. The recommended oral dose is 100 mg twice a day.

The safety and efficacy of Pletal has been evaluated in several clinical trials. This NDA contains several clinical and pharmacokinetic (27 *in vivo* and 10 *in vitro*) studies. The to-be marketed formulation is same as the one used in the Phase III clinical trials. The only difference is in the shape of the 50 mg strength. Clinical trials used a round 50 mg tablet while the proposed tablet is triangular in shape. Dissolution testing has been conducted to demonstrate that these two tablets (different shapes) are equivalent.

The parent cilostazol and two of its major metabolites are active. According to the sponsor, based on in vitro data, OPC-13015 (3,4-dehydro cilostazol) is 3 to 7 times more potent than cilostazol and OPC-13213 (4'-trans-hydroxy cilostazol) is 2 to 3 times less potent than cilostazol. All these three moieties have been monitored in the PK studies. The plasma AUC of OPC-13015 and OPC-13213 are 28% and 9% that of cilostazol. The absolute bioavailability of cilostazol is unknown. The relative bioavailability of cilostazol tablet compared to oral suspension is 100%.

The sponsor has adequately validated the assay methodology for cilostazol and its major metabolites. The sponsor also adequately characterized the pharmacokinetics (single and multiple dose) of cilostazol in healthy volunteers, hepatically impaired patients and renally impaired patients. Pharmacokinetics were also studied in patients with intermittent claudication. Effect of age and gender were also investigated. Metabolic enzymes (cytochrome P450 isozymes) responsible for cilostazol metabolism have been identified. About 74% of the cilostazol dose administered is excreted in urine (mostly as metabolites) and about 21% in feces.

No unchanged drug is found in urine. Absolute bioavailability information on the tablets is not available. Cilostazol is absorbed rapidly with a t_{max} of about 3 hours. Cilostazol has a half-life of about 11 hours. It is highly protein bound (>95%). The pharmacokinetics of cilostazol appear to be non-linear over a dose range of 50 to 200 mg with less than proportional increase in Cmax with dose. At steady state, accumulation index for cilostazol was 1.7, for OPC-13015 was 3.1 and for OPC-13213 was 2.5 compared to single dose. Food significantly increased the C_{max} of cilostazol by 91% and AUC by 24%. In mild hepatic impairment, there were no significant changes in the pharmacokinetics of cilostazol and its metabolites after single dose administration. In renal impairment, there was no significant effect on cilostazol and OPC-13015 pharmacokinetics. A significant increase in OPC-13213 Cmax and AUC at steady state (+173 and +209%) in patients with severe renal impairment was observed. No dosage adjustment but caution is necessary in renally impaired patients. Pharmacokinetics of cilostazol were similar in intermittent claudication patients and normal volunteers. No significant age and gender effects were observed. The PK-PD relationship of cilostazol has been summarized by the sponsor.

Cilostazol is primarily metabolized by CYP3A4 with minor metabolism by CYP2C19, CYP1A2, CYP2B6, CYP2D6 and CYP2E1. Coadministration of cilostazol and warfarin did not result in any changes in pharmacokinetics and pharmacodynamics of warfarin. Concomitant administration of cilostazol and erythromycin resulted in a significant increase in Cmax and AUC of cilostazol. Administration of cilostazol with quinidine did not inhibit the metabolism of cilostazol. Coadministration of omeprazole with cilostazol increased the Cmax and AUC of OPC-13015 by 29 and 69% accompanied by a slight increase in Cmax and AUC of cilostazol. Coadministration of cilostazol with aspirin resulted in significant increases in ADP induced platelet aggregation. In vitro inhibition studies carried out using human liver microsomes indicate that cilostazol inhibits metabolic reactions catalyzed by cytochrome P450 2C9 and 2C19. While one study indicates possible inhibition of CYP3A4-mediated metabolism, the results of all in vitro studies are not very clear. Caution is therefore necessary when cilostazol and CYP3A4 substrates are concomitantly administered.

A non-parametric population PK analysis conducted by the sponsor indicated that the PK of cilostazol is decreased (clearance increased) in smokers and is also affected by concomitant administration of diltiazem (increased cilostazol exposure).

RECOMMENDATION: The present submission (NDA 20-863) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics. The submission is acceptable provided that a) labeling comments # 1 - 13 and b) comment to sponsor # 5 are adequately addressed by the sponsor. A biowaiver can be granted for the to-be marketed 50 mg tablet based on comparable dissolution data between the to-be marketed tablet and the clinical tablet formulation. The dissolution method selected by the sponsor are acceptable. However, the dissolution specification for cilostazol should be changed

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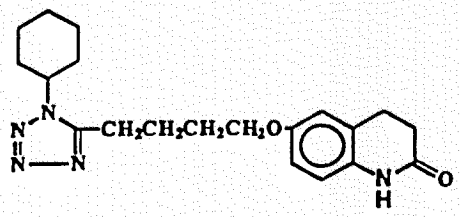
II. BACKGROUND

Pletal® tablets contain cilostazol (50 mg and 100 mg) with potent antiplatelet as well as vasodilating activity. This drug is a 3,4-dihydro quinolinone derivative, formulated as immediate release tablets of 50 and 100 mg strengths for oral administration. Cilostazol product is manufactured by Otsuka Pharmaceutical Co., Ltd. in Tokushima, Japan.

Due to the antiplatelet, vasodilative effects and positive effects on plasma lipoproteins, this drug has potential for beneficial effects on ameliorating intermittent claudication. The sponsor has proposed to market the Pletal tablets at a dosage strength of 50 and 100 mg. The proposed indication for Pletal is for amelioration of symptoms in patients with intermittent claudication secondary to peripheral arterial disease of the lower extremities. The proposed dose is 100 mg tablet to be taken twice a day without food (on empty stomach). Pletal tablet is a white, round (100 mg) and triangular (50 mg), debossed tablet.

STRUCTURE OF DRUG ENTITY: Cilostazol is chemically 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone with a molecular weight of 369.47. Cilostazol is

achiral, and has no polymorphs, with the structure shown in figure below.



CILOSTAZOL

SOLUBILITY CHARACTERISTICS: Cilostazol is poorly soluble in water at all pH values in the range

III. FORMULATION: The formulation of the clinical and to-be marketed tablet are the same. The details of the tablet formulation for the 50 and 100 mg strengths are given below.

CILOSTAZOL TABLET FORMULATION (mg/tablet)

INGREDIENT	50 mg tablet	100 mg tablet
Cilostazol Corn starch, NF Microcrystalline cellulose, NF Carboxymethylcellulose calcium, NF Hydroxypropyl methylcellulose 2910, USP Magnesium stearate, NF Purified water*, USP	50.0 mg	100.0 mg
Total tablet weight		

* Purified water is removed in the process of drying.

IV. PHARMACOKINETICS AND BIOAVAILABILITY:

The summary of pharmacokinetics of cilostazol and its active metabolites OPC-13015 and OPC-13213 are provided here.

a. ABSOLUTE BIOAVAILABILITY (and RELATIVE BIOAVAILABILITY):
Pharmacokinetics of cilostazol have not been determined following intravenous route of administration. Hence, information on absolute bioavailability is not available. However, information from mass balance study, where radiolabeled drug was administered, indicates that at

least 74% of administered drug (as parent and metabolites) crossed the gastrointestinal barrier (based on radiolabel in urine). Information on relative bioavailability can be obtained from a relative bioavailability study where an oral suspension arm was included. It was found that bioavailability of the tablets relative to the oral suspension was 100% based on AUC of cilostazol.

b. ABSORPTION: Following oral doses up to 200 mg (either via single or multiple administration) in healthy volunteers, cilostazol was absorbed rapidly.

c. DISTRIBUTION: The true volume of distribution was not estimated due to non-availability of an intravenous formulation.

Plasma protein binding: In vitro protein binding studies indicate that binding is independent of cilostazol concentrations in the range of 0.25 to 5 μg/ml. Cilostazol is >95% bound to plasma proteins. Cilostazol binds primarily to albumin.

d. ELIMINATION (METABOLISM AND EXCRETION):

Terminal phase half-life: Half-life of cilostazol is approximately 11 hours in healthy male volunteers. Elimination half-life of OPC-13015 is similar to cilostazol. The elimination half-life of OPC-13213 is slightly longer (about 14 hours). Mean Cl/F was found to be 140 ml/hr/kg. A secondary peak in cilostazol plasma concentration-time profile (possibly due to enterohepatic recycling) has been observed in few subjects. The secondary peak occurred at different times in different subjects (generally after about 20 hours).

Metabolism: Cilostazol is highly metabolized as indicated by no unchanged drug found in urine upon oral administration.

Enzymes responsible for metabolism of cilostazol have been identified. It is metabolized primarily by cytochrome P450 3A4. It was found that CYP2C19 and possibly CYP1A2, CYP2B6, CYP2D6 and CYP2E1 are involved in the metabolism of cilostazol. The metabolic pathway for cilostazol is shown in the following figure:

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Excretion: Upon administration of single 50 mg dose of radiolabeled cilostazol as oral ethanolic solution, mean cumulative urinary and fecal recoveries of total radioactivity were 74% and 21% respectively. No unchanged drug was detected in urine. This indicates that most of cilostazol is excreted as metabolites. The terminal half-life of radioactivity was about 4 hours and half-life of cilostazol was about 2.5 hours. Comparison of this half-life to the half-life obtained after administration of tablet indicates that cilostazol pharmacokinetics are absorption (or dissolution) rate limited. Renal clearance of OPC-13213 is about 250 ml/min in healthy volunteers after dosing with 50 mg cilostazol.

e. DOSE PROPORTIONALITY: When studied at three single dose levels of 50, 100 and 200 mg cilostazol administered as multiple units of 50 mg tablets (study 21-93-204), the pharmacokinetics of cilostazol and its metabolites are non-linear. The non-linearity is more pronounced for Cmax than AUC. A four-fold increase in dose resulted in only a 2-fold increase in Cmax and a 3-fold increase in AUC of cilostazol. This indicates that with increase in cilostazol dose, a lower fraction of cilostazol may be absorbed.

f. FOOD EFFECT: Food (a high fat meal) increased cilostazol C_{max} by 91% (90% confidence interval 166.7 - 200.7) and AUC by 24% (90% confidence interval 119.1 to 148.5) when cilostazol 100 mg tablet formulation was administered within 0.5 hours after high fat breakfast (21-93-204). Similar increases were also observed in metabolite concentrations. Another food effect study 011808 conducted on the 50 mg tablet also showed similar results. This food effect could be due to increased solubilization and further increased absorption of cilostazol. Hence, cilostazol should be taken on an empty stomach (fasted state).

g. SPECIAL POPULATIONS:

Age: Study 21-93-202 was conducted to study the effect of age on pharmacokinetics of cilostazol and its active metabolites. Age-related effects were analyzed by comparing 3 age groups (50 - 59 years, 60 - 69 years and ≥ 70 years). No significant age effect was found on the pharmacokinetics of cilostazol and its metabolites.

Gender: Study 21-93-202 conducted in women and men of the same age (3 age groups in age range of 50 to >70 years) indicates that there is no significant gender effect on the pharmacokinetics of cilostazol and its metabolites. However, a trend towards higher plasma concentrations and greater adverse effects was observed in females compared to males. This trend should be compared to the data from pivotal clinical trials.

Hepatic impairment: Pharmacokinetics of cilostazol and its major metabolites were studied after administration of 100 mg single dose of cilostazol to patients with impaired liver function belonging to Child-Pugh class A and B and corresponding matched normal subjects. There were no significant differences in cilostazol concentrations in hepatically impaired subjects compared to normal controls. Mean AUC of OPC-13213 decreased about 13% and that of OPC-13015 increased 25% in hepatically impaired patients compared to normal subjects. These small differences may not be clinically significant. Hence, dose-adjustment is not necessary in these patients. However, patients with moderate and severe hepatic impairment (that have not been

studied here) should be carefully monitored when cilostazol is administered to these patients, unless suitable clinical data is available in these patients.

Renal impairment: This is a multiple dose study carried out in subjects with mild (Cl_{cr} 50 - 89 ml/min), moderate (Cl_{Cr} 26 - 49 ml/min) and severe renal impairment (Cl_{Cr} 5 - 25 ml/min) along with matched healthy controls. Subjects with renal insufficiency who are undergoing dialysis were not permitted in this study. PK of cilostazol was found to be similar in patients with renal impairment and normal subjects except for free fraction being higher in severe renal disease group. Although not statistically significant, the cilostazol Cmax and AUC were lower in severe renal disease group at steady state by 29 and 39%. Unbound cilostazol clearance was 59% higher in the severe renal disease group. Since unchanged cilostazol is not excreted in urine, this difference could be due to alteration in protein binding or hepatic metabolism. Similarly, the OPC-13015 Cmax and AUC were 41 and 47% lower in severe renal disease group compared to normal subjects. A significant increase in OPC-13213 Cmax and AUC at steady state was observed with a change of +173% and +209% in subjects with severe renal impairment. Based on relative exposure of cilostazol and its metabolites and their relative potency, no dosage adjustment is necessary in patients with renal impairment. However, caution should be exercised when administering cilostazol to patients with renal impairment since the relative potency based on safety of each moiety is not well known. Also, the effect of dialysis on PK of cilostazol and its metabolites has not been established.

PK in patients: Pharmacokinetics of cilostazol and its metabolites in healthy volunteers were found to be similar in patients with intermittent claudication.

Effect of smoking: Population pharmacokinetic analysis indicates that cilostazol exposure was 18% lower in smokers than nonsmokers.

h. BIOEQUIVALENCE BETWEEN FORMULATIONS:

The clinical and to-be marketed formulation composition is identical.

The pivotal clinical trials utilized a round 50 mg tablet. The sponsor wants to market the same 50 mg tablet formulation A waiver of a bioequivalence study between the clinical and to-be marketed tablet is granted based on in vitro dissolution data

Dosage form proportionality: The 50 and 100 mg strengths are not compositionally proportional. The relative bioavailability/bioequivalence study 21-93-205 indicates that the 50 and 100 mg strengths are comparable but not bioequivalent based on parent cilostazol (90% confidence interval on cilostazol Cmax: 79 - 98). However, these dosage strengths are bioequivalent based on the two active metabolites.

VI. PHARMACODYNAMICS:

PK-PD: The mechanism of action of cilostazol in exerting beneficial effects on the symptoms of intermittent claudication is not fully understood. However, it is known that this drug inhibits platelet aggregation. With the existing data, for exploratory purposes, the sponsor made an attempt to correlate plasma concentrations to % inhibition in platelet aggregation. Extensive data analysis has not be provided. The doses studied in clinical trials were based on the effect of cilostazol doses on platelet aggregation.

POPULATION PHARMACOKINETICS: The sponsor utilized a nonparametric population pharmacokinetic approach since an irregular secondary peak in the PK profile of cilostazol was observed. During a previous meeting with the sponsor, it was mentioned that this type of analysis will be considered exploratory until appropriately validated. The sponsor was also asked to use a semi-parametric method for analysis of this data. Based on the non-parametric analysis, only smoking status and diltiazem concomitant use were identified as potentially important covariates. Cilostazol exposure was 18% lower in smokers than nonsmokers. Concomitant administration of diltiazem increased cilostazol exposure by 53%. This result agrees with the expectations based on results from the in vitro metabolism study as well as the drug interaction study with erythromycin.

VII. DRUG INTERACTIONS:

a. In-vitro inhibition studies in human liver microsomes and recombinant systems: These studies indicate that the parent cilostazol did not inhibit reactions catalyzed by human cytochrome P450 1A2, CYP2D6, CYP2E1 or CYP2B6. Cilostazol, however, inhibited cytochrome P450 2C9 (tolbutamide hydroxylation) with a lowest Ki value of 23.8 μM and CYP2C19 with a Ki of 44 μM. Considering the expected Cmax of Cilostazol of 3 μM, the inhibition of CYP2C9 and CYP2C19 may not be significant. Inhibition of CYP3A4 mediated metabolism is variable. The study in human liver microsomes indicates that cilostazol does not inhibit CYP3A4 mediated metabolism, however the two studies in recombinant systems indicate a Ki of about 6 and 19 μM. This indicates that there may be a potential for interaction with CYP3A4 substrates.

Another in vitro interaction study with S-warfarin indicated that the parent cilostazol does not inhibit S-warfarin metabolism at therapeutically relevant concentrations. The Ki values of 97 to 144 μM indicates that clinical interaction between cilostazol and S-warfarin is likely to occur

only at high concentrations of cilostazol.

b. In-vitro protein binding interaction studies: Omeprazole and warfarin cause a significant displacement of cilostazol from protein binding sites. Similarly, cilostazol and its metabolites cause a significant displacement of warfarin from its protein binding sites.

c. In-vivo drug interaction studies:

Warfarin: A two-way crossover study of single doses of warfarin (25 mg) with multiple dosing of either cilostazol (100 mg bid) or placebo in 20 healthy male volunteers indicated that cilostazol 100 mg bid administered for 13 days did not have any effect on the pharmacokinetics of R and S-warfarin and pharmacodynamics (PT, APTT and bleeding time) of single dose of warfarin.

Erythromycin: A fixed sequence, multiple dose erythromycin and single dose cilostazol study in 16 healthy male volunteers indicated that coadministration of 100 mg cilostazol as single dose after 500 mg erythromycin q8 hours given for 7 days (and also during cilostazol elimination) resulted in a statistically significant increase in cilostazol Cmax by 47% and AUC by 74%. Percent of cilostazol excreted in urine increased by 50%. The magnitude of drug interaction upon concomitant administration of cilostazol and erythromycin as multiple doses may be different and cannot be easily predicted from single dose data. This study indicates that concomitant administration of potent inhibitors of CYP3A4 mediated metabolism of cilostazol, such as ketoconazole, can result in significant increases in parent cilostazol concentrations. Careful monitoring and dosing adjustments might be necessary in patients taking CYP3A4 inhibitors concomitantly with cilostazol.

Quinidine: A crossover single dose study in 14 healthy male and 8 female volunteers indicated that coadministration of 200 mg quinidine with 100 mg cilostazol resulted in a small decrease in Cmax and AUC of cilostazol and its metabolites (14%, 17% and 18% decrease in Cmax and 11%, 12% and 30% decrease in AUC of cilostazol, OPC-13015 and OPC-13213). This could be due to possible effects on cilostazol absorption. Coadministration of quinidine with cilostazol does not inhibit the metabolism of cilostazol.

Omeprazole: A fixed sequence multiple dose omeprazole and single dose cilostazol study in 10 healthy male and 10 female volunteers indicated that coadministration of 40 mg omeprazole qd for 12 days with single 100 mg cilostazol resulted in a small but significant increases in parent cilostazol (Cmax increased 14% and AUC increased 24%) and OPC-13015 (26% increase in Cmax and 64% increase in AUC). The OPC-13213 levels were decreased. This indicates that coadministration of potent CYP2C19 inhibitors with cilostazol can result in small but significant drug interactions. Hence, caution is recommended, by the sponsor, for coadministration of these drugs with cilostazol.

Aspirin: A crossover multiple dose design study in 12 healthy male volunteers receiving cilostazol 100 mg bid and aspirin 325 mg qd resulted in small increases in plasma concentrations of cilostazol and its major metabolites. No clinically significant interactions were noted between

cilostazol and aspirin with respect to PT, APTT and bleeding time. Significant differences in ADP induced platelet aggregation were observed upon concomitant administration.

Diltiazem: Results of population pharmacokinetic analysis indicate that concomitant administration of diltiazem increased cilostazol exposure by 53%. This result agrees with the expectations based on results from the in vitro metabolism study as well as the drug interaction study with erythromycin.

VIII. ANALYTICAL METHODS VALIDATION: All the studies (expect one) conducted to determine pharmacokinetics of cilostazol and its metabolites, in US, utilized a single assay conducted at one laboratory for determining concentrations of cilostazol and its metabolites in plasma and urine One study utilized an assay conducted at Both these assays were adequately validated. Adequate information regarding stability of samples in human plasma during storage and through freeze/thaw cycles has been provided. Further, assay performance within each study has also been submitted.

COMMENTS TO THE MEDICAL OFFICER:

1. Cilostazol is metabolized primarily by cytochrome P450 3A4. The drug interaction study conducted with erythromycin indicates a significant interaction. A multiple dose of 500 mg erythromycin (as base, Ery-tab) q8 hours with single dose of 100 mg cilostazol resulted in a statistically significant increase in cilostazol Cmax by 47% and AUC by 74%. Percent of cilostazol excreted in urine increased by 50%. The magnitude of drug interaction upon concomitant administration of cilostazol and erythromycin as multiple doses may be different and cannot be easily predicted from single dose data. This study indicates that concomitant administration of potent inhibitors of CYP3A4 mediated metabolism of cilostazol, such as ketoconazole, can result in significant increases in parent cilostazol concentrations. Careful monitoring and dosing adjustments might be necessary in patients taking CYP3A4 inhibitors concomitantly with cilostazol.

2. Cilostazol is a weak inhibitor of drug metabolism by CYP2C9 and CYP2C19. In an in vivo study, no significant drug interaction was found upon concomitant administration of cilostazol and warfarin. However, only single doses of warfarin were studied. Hence, it may be necessary to evaluate the safety of concomitant multiple dosing of cilostazol and warfarin from the clinical database.

3. There were no significant differences in cilostazol concentrations in hepatically impaired subjects (mild impairment) compared to normal controls. Mean AUC of OPC-13213 decreased about 13% and that of OPC-13015 increased 25% in hepatically impaired patients compared to normal subjects. These small differences may not be clinically significant. Hence, dosage adjustment is not necessary in these patients. However, patients with moderate and severe hepatic impairment (that have not been studied here) should be carefully monitored when

cilostazol is administered to these patients, unless suitable clinical data is available in these patients.

4. The pharmacokinetics of cilostazol and its active metabolites have been studied in patients with mild, moderate and severe renal impairment. However, this study did not include patients on dialysis. There was a significant increase in Cmax and AUC of OPC-13213 in patients with severe renal impairment. Based on relative exposure of cilostazol and its metabolites and their relative potency, no dosage adjustment is necessary in patients with renal impairment. However, caution should be exercised when administering cilostazol to patients with renal impairment since the relative potency based on safety of each moiety is not well known. Also, the effect of dialysis on PK of cilostazol and its metabolites has not been established.

5. Race effect: Most of the pharmacokinetic studies were conducted in caucasian subjects (volunteers mostly from U.S., few from U.K. and Germany). PK studies conducted in Japan did not provide much information since only summaries were submitted. Hence, adequate comparisons for race effect on metabolism of cilostazol cannot be made.

6. In vitro studies in human liver microsomes indicate that cilostazol does not inhibit drug metabolism by CYP3A4. However, other in vitro studies using recombinant in vitro systems indicate that cilostazol at higher concentrations (with a Ki twice the therapeutically achievable concentrations) may inhibit metabolism of CYP3A4 substrates. Hence, caution may be warranted when cilostazol is administered with CYP3A4 substrates like cisapride. However, the inhibition data available is not confirmatory. We request the medical officer to evaluate the clinical database to see if any adverse events were observed with concomitant administration of cilostazol and CYP3A4 substrates like cisapride, calcium channel blockers, lipid lowering drugs like simvastatin etc.

COMMENTS TO THE SPONSOR:

1. In future, the in vivo drug interaction studies should include the most potent inhibitors for CYP3A4. Further, when an interaction study is conducted, it is recommended that the pharmacokinetics of both drugs be determined. This helps in evaluation of the effects of both drugs on each other.

2. The standard curve plots in the assay methodology should plot concentration (independent variable) on X-axis and the peak height or area ratio (dependent variable) on Y-axis.

3. The sponsor should generally evaluate the effects of dialysis (in severe renal impairment) on pharmacokinetics of the drug being studied, in future.

4. In future, in vitro metabolism studies should employ therapeutically relevant concentrations of the drugs studied. Further, evaluation of the inhibition potential of major metabolites of the drugs should also be considered.

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Clinical Pharmacology & Biopharmaceutics' Briefing 06/16/98 (Attendees: Lesko, MChen, Malinowski, Marroum, Al-Habet, Huang, Karkowsky, Parmelee, Selen).

RD/FT initialed by Patrick J. Marroum, Ph.D. 6/16/1998

cc: HFD-110: NDA 20-863; Division file; Buehler; HFD-870: Venkata Ramana S. Uppoor; HFD-340: Viswanathan; CDR: Attn: Barbara Murphy.