CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-863

MEDICAL REVIEW(S)

BUEHLER
AUG 13 1998

U. S. PUBLIC HEALTH SERVICE

Steven Mark Rodin, M.D.
Medical Officer

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiorenal Drug Products

Addendum #1 to Medical Review of NDA

Reviewer:	Steven M. Rodin, M.D.
addendum last revised:	3 August 1998
NDA #:	**20-863**
Sponsor:	Otsuka America Pharmaceutical, Inc.
Drug:	**cilostazol** (Pletal®)
Proposed indication:	symptomatic intermittent claudication
Date of NDA submission:	19 September 1997
Date of original review:	27 July 1998

1. **Bleeding risk as a function of Aspirin co-exposure:**

In a submission of 7/27/98 the sponsor clarified the NDA experience with co-administration of cilostazol (CLZ) and aspirin (ASA). They reported no conclusive evidence of interaction in an analysis subject to random and systematic errors arising from the small numbers of events as well as from the nonrandom allocation of ASA. The analysis pooled subjects exposed to ASA in the 8 largest placebo-controlled trials. ASA was used in 201 CLZ-randomized subjects (largely in the 200 mg/d group) and 190 placebo subjects.[1] Bleeding events were compiled by an adequate method of aggregation of COSTART terms. In the largest, i.e. 200 mg/d, group the crude mean rate of bleed was comparable in those exposed and not exposed to ASA (6.90 and 6.92%, respectively, based on 12 and 57 events, respectively). Events were too few in the other groups to provide even modestly reliable inferences on the basis of mean results.

[1] in the majority of the studies, subjects were to have been excluded if they required the uninterrupted use of ASA.

2. First safety update

The data in the first safety update (submitted 1/29/98; extending the original NDA cutoff one year, i.e. to 9/2/97) were in large part superceded by the subsequent analyses submitted within sources already analyzed in my original NDA review of 7/27/98, i.e. the final report of study 21-96-202; the final report of study 21-94-301; and the revised integrated summary of safety.

A total of 9 deaths (occurring while on drug or within the 30 day post-treatment window) are newly reported in uncontrolled 21-91-201 study. These are here enumerated by attributed cause, identification number, previous trial enrollment, and uncontrolled daily CLZ exposure:

Cardiac Arrest: #0478 (21-94-201/21-91-201; >100 to ≤200 mg)
Coronary Artery Disorder: #0254 (21-94-203/21-91-201; >200 to ≤300 mg)
Congestive Heart Failure: #0413 (21-94-201/21-91-201; >100 to ≤200 mg)
MI: #0019 (21-92-202/21-91-201; >300 mg)
MI: #0555 (21-92-202/21-91-201; >100 to ≤200 mg)
MI: #0190 (21-94-201/21-91-201; >100 to ≤200 mg)
Lung Carcinoma: #0331 (21-92-202/21-91-201; >100 to ≤200 mg)
Lung Disorder: #0070 (21-94-201/21-91-201; >200 to ≤300 mg)
Carcinoma: #0210 (21-94-203/21-91-201; >200 to ≤300 mg)

From clinical trials in Japan (11 trials were completed/ongoing) there was one new serious adverse event (AE), a cerebral infarction occurring in a 56 year old male diabetic retinopathy patient (subject 2807607) in study PUO94001. He had received CLZ 150 mg/d for 16 days at which time he had a stroke.

From post-marketing studies in Japan (41 trials) and other Asian and South American countries (21 trials) there were 12 adverse events newly reported which were attributed as serious by the attending physician. Not all of these cases met FDA's criteria for seriousness. The types of events were GI hemorrhage, cardiac failure, myocardial infarction, sinus tachycardia, sudden death, cerebral haemorrhage, cerebrovascular disorder, epistaxis, nephropathy, and pulmonary carcinoma.

No serious adverse events were reported in the post-marketing studies conducted in other Asian and South American countries during the reporting period.

Steven Mark Rodin, MD 8/3/98

Steven Mark Rodin, M.D. Date
Medical Officer

cc: HFD-110/ division file, CSO, A. Karkowsky, **no copy to S.Rodin**

Memo

to: Avi Karkowski
from: Steve Rodin
date: 12 August 1998

re: **Cilostazol effect on lipids**

Here is a summary of findings. The placebo-corrected point estimates fairly consistently show small increases from pre-treatment HDL (3-4 mg/dL), and modest decreases from pre-treatment TG (more often amounting to 30-60 mg/dL, but in some studies the mean decreases were <20 mg/dL). Changes in LDL were said to be small.

I have seen no mention of similar findings in the amrinone or milrinone labels. I have asked John Koerner to comment on biologic plausibility with respect to known PDE III receptor pharmacology.

Table: 1

Placebo-corrected mean changes in lipid parameters from baseline to end of 200 mg/d CLZ exposure in the 8 largest placebo-controlled trials[1]

	study 21-92-202	*study* 21-96-202	*study* 21-94-201	*study* 21-94-203	*study* 21-95-201	*Study* 21-93-201[2]	*study* 21-90-201	*study* 21-94-301
HDL	3.8	4.1	4.2	3.7	3.1	4.1	3.4	0.11 mmol/L
TG	-35.6	-28.3	-17.3	-12.4	-50.7	-28.1	-60.6	-0.7 mmol/L

S.Rodin

Steven Mark Rodin, M.D.
Medical Officer

8/12/98
Date

cc: HFD-110/ division file, CSO, J. Koerner A. Karkowsky, **no copy to S.Rodin**

[1] units are mg/dl unless otherwise shown..
[2] HDL and TG changes in this study were reportedly associated with a p value of 0.0001.

G. Buchler

JUL 27 1998

U. S. PUBLIC HEALTH SERVICE

Steven Mark Rodin, M.D.
Medical Officer

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiorenal Drug Products

Medical Review of NDA

1 General information

Reviewer:	Steven Mark Rodin, M.D.
Review last revised:	27 July 1998
NDA #:	20-863
Sponsor:	Otsuka America
Drug:	cilostazol (Pletal®)
Proposed indication:	intermittent claudication
related IND:	
Date of NDA submission:	19 September 1997
Latest data submission:	6 July 1998

TABLE OF CONTENTS

[cont] TABLE OF CONTENTS

[cont] TABLE OF CONTENTS

[cont] TABLE OF CONTENTS

3 BACKGROUND

1 General Background

Cilostazol (CLZ) is a synthetic antiplatelet and vasodilating agent whose previous code name was OPC-13013. This drug was approved in Japan in 1988 for the treatment of various ischemic symptoms, and subsequently was approved in 5 other countries in eastern Asian, as well as in Argentina.

Japan's labeling reportedly contraindicates the drug's use in patients with known hemorrhage, and cautions about concomitant use of warfarin or ticlopidine (because of observed drug-related deaths from gastric hemorrhage in such scenarios). In postmarketing experience through early 1994, reportedly the most frequently reported adverse event (AE) associated with cilostazol was headache.

3.2 Abbreviations and Operational definitions

ACD= absolute claudication distance
BP= blood pressure
CAD= coronary artery disease
CHF= congestive heart failure
CLZ= cilostazol
EKG= electrocardiogram
IC= intermittent claudication
ICD= initial claudication distance
MI = myocardial infarction
PTX= pentoxifylline
OXP= oxpentifylline

Absolute claudication distance (ACD) = total symptom-limited walking distance.

Claudicant = a person who experienes the symptom of intermittent claudication.

Initial claudication distance (ICD) = walking distance at claudication onset.

Intermittent claudication (IC) = exertional lower extremity pain[1] which limits walking tolerance, and abates with rest.

[1] or cramp, or severe fatigue.

4 CHEMISTRY

Cilostazol is formally named 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2-(1H)-quinolinone). See the chemist's review for a detailed discussion of chemistry.

5 PRECLINICAL PHARMACOLOGY

See the pharmacologist's review for a detailed discussion of pre-clinical pharmacology. Briefly, CLZ reportedly prevents platelet aggregation through reversible inhibition of cyclic AMP phosphodiesterase III. After discontinuation of CLZ, platelet function reportedly returns to normal by 96 hours, without rebound changes in platelet concentrations. This drug also reportedly causes vasodilation by enhancing the effect of endogenous vessel wall prostaglandin PGI2, and has putative lipid-modifying effects.

Coronary arteritis and endocardial hemorrhage and/or hemosiderin deposition and fibrosis in the left ventricle was observed in the beagle dog exposed to CLZ doses of 30 mg/kg/d. Reportedly these abnormalities have also been observed in beagle dogs exposed to other vasodilators (e.g., minoxidil and milrinone).

6 CLINICAL PHARMACOKINETICS:

e the Biopharmaceutical review for detailed discussions of clinical pharmacokinetics and ..etabolism. Briefly, CLZ is largely protein bound (>90%) at concentrations of 0.25-5 ug/mL. The half-life of parent drug is approximately 11 hours. After oral administration of parent drug, CLZ is reportedly the predominant species found in plasma (56% of total analytes), followed by the metabolites OPC-13015 (15% of total) and OPC-13213 (4% of total). OPC-13015 is suggested to plausibly contribute to the pharmacologic effects of CLZ, based on its plasma concentration, unbound fraction, and pharmacologic potency. The half-lives of OPC-13015 and OPC-13213 are approximately 11 and 14 hours, respectively. There are no estimates of CLZ's volume of distribution or absolute bioavailability.

7. CLINICAL PHARMACOLOGY:

See Dr. Karkowsky's review for assessments of the clinical pharmacology data.

8 LARGE PLACEBO-CONTROLLED EFFICACY TRIALS:

8.1 Study 21-92-202:

1.1 @Design Summary

This concurrent placebo-controlled, double-blind, parallel-group study randomized (in a 1:1 ratio) 516 subjects (atherosclerotic peripheral arterial disease (PAD) patients with moderately severe, stable, intermittent claudication) to receive placebo, or cilostazol given as a fixed 100 vs 200 mg/d dose in equally-divided twice-daily (50 or 100 mg bid) oral administrations for 24 weeks. The objectives were to assess safety (by observing, for example, cardiovascular morbidity and all-cause mortality), and improvement in ICD and ACD, at trough, after 24 weeks of therapy.

The chronology of this study's execution was reportedly as follows:

Table: 1

@Chronology of the execution of Study 21-92-202

Event Completed	Date
Original Protocol	10/26/92
1st Amendment	1/25/93[2]
2nd Amendment	3/12/93
3rd Amendment	3/12/93
4th Amendment	3/12/93
1st subject randomized	4/8/93
IND submission of 1st Amendment	4/9/93
Last Subject's Final Follow-up	10/14/94
Final Analysis	6/27/97

[source: submissions dated 10/22/97; and 7/6/98-A]

order to increase the sample size for the analysis of cardiovascular morbidity and all-cause ...ortality, the protocol was amended (Amendment 1) to allow certain centers to observe patients for these safety outcomes without assessing postrandomization walking distances (pre-treatment walking distances were still to be captured in order to assure that enrollment criteria had been uniformly satisfied). The following centers enrolled subjects under this amendment: 005, 009, 013, 026, 029, 031, 032 and 040.

With the exception of center 32, none of these Amendment 1 centers contributed any subjects to the efficacy analysis. The sponsor reports that center 32 initiated the study under the original protocol, and then subsequently changed to Amendment 1. This center enrolled 8 subjects under Amendment 1 and, as intended, captured not post-randomization walking distance data but rather only safety data.

The center also enrolled 6 other subjects (two each were randomized to placebo, CLZ 50 mg bid, and CLZ 100 mg bid, respectively) under the original protocol, and thus should have captured sequential walking distance data in them. Yet, for unclear reasons only 1 post-randomization walking distance datum is reported in these 6 subjects (at approximately six months). Among other centers in which the trial was operating under Amendment 1, reportedly no subjects had post-randomization walking test data available for analysis.

[2] not submitted to IND until 4/9/93

The blind was reportedly broken for three patients: 1) patient 146 (CLZ 50 mg) unblinded on 12/15/93 due to death, 2) Patient 236 (placebo) unblinded on 12/14/93 due to hospitalization for stained ventricular tachycardia, and 3) Patient 305 (placebo) unblinded on 12/21/93 due to sudden death.

8.1.2 @**Enrollment criteria.** (study 21-92-202)

Adult subjects (at least 40 years old) of both sexes were eligible for enrollment if they had atherosclerosis obliterans-induced intermittent claudication which was chronic (at least 6 months), stable (without significant change within the past 3 months), and not associated with lower extremity ischemic rest pain, ischemic ulceration, or gangrene. To qualify for randomization, enrolled subjects had to meet additional qualifying criteria related to symptom severity, specificity, and invariability (see below discussion of qualifying criteria).

Additional bases for exclusion from enrollment were the following:

- female of childbearing potential, unless surgically sterilized, or at least 1 year postmenopausal.
- sympathectomy or lower extremity arterial reparative surgery, including endovascular procedures, within the previous 3 months.
- greater than 60% above ideal body weight.
- treated supine arterial blood pressure (BP) >200 mmHg systolic or >100 mmHg diastolic.
- current metastatic malignancy.
- deep vein thrombosis within the past 3 months, other than isolated calf vein thrombosis.
- history or current evidence of concomitant exercise-limiting disease other than intermittent claudication. For example, such conditions as congestive heart failure (CHF), myocardial infarction (MI) within 6 months or incomplete recovery from an MI which occurred > 6 months, symptomatic cardiac arrhythmias, angina pectoris, and orthopedic conditions.
- risk of, or tendency to, bleeding.
- clinically significant hematologic disease, twice the normal values for AST or ALT, serum creatinine > 2.5 mg/dL.
- current alcohol or other drug abuse, or use of an investigational drug within the past 30 days.
- a requirement for the uninterrupted use of medications that have a significant antiplatelet, anticoagulant, vasoactive (with the exception of occasional use of nitroglycerin or isosorbide dinitrate, or unchanged doses of calcium channel blockers), hemorrheologic (including pentoxifylline) or NSAID activity (with the exception of diclofenac sodium).

8.1.3 @**Qualifying criteria.** (study 21-92-202)

After enrollment there was to be at least a 3 week lead-in period during which subjects were to be discontinued from prohibited medications. Subjects then qualified for randomization if the following observations were obtained during standardized treadmill testing conducted prior to study treatment:

- attainment of 30-200 meter initial claudication distance on the last 2 of up to 3 visits (spaced 3-7 ys apart), with no greater than 25% variation between the last two visits.
.est terminated for intermittent claudication only.
- exercise-induced 10 mmHg decrease in estimated BP of at least one ankle artery, measured one minute following the end of symptom-limited treadmill testing.
- supine Doppler ankle brachial index[3] (ABI) of 0.90 after 10 minutes at rest, or resting great toe brachial index (TBI) of 0.70 in those with incompressible peripheral arteries.

8.1.4 @**Treatment regimen.** (study 21-92-202)

Qualified subjects were to undergo double-blind randomization to placebo, or cilostazol given as fixed 50 or 100 mg bid oral administrations for 24 weeks. The CLZ formulation was (a 50 mg tablet, produced in lots 2J-75-PP1 and 2J-76-PB1) was the same as the final market formulation. Dummy medication was given in the low dose CLZ regimen (i.e. one placebo tablet and one 50 mg CLZ tablet) in order to maintain the blind. Patients were to take their doses 30 minutes before breakfast and 30 minutes before dinner, except the night before a clinic visit, when they were to take their second dose between 8:00 pm and 11:00 pm.

Concomitant use of calcium channel blockers was allowed at unchanged doses, as was occasional .e of nitroglycerin or isosorbide dinitrate. An attempt was to be made to keep constant other supportive interventions for vascular disease such as moderate exercise and abstention from tobacco smoking.

8.1.5 @**Endpoints.** (study 21-92-202)

8.1.5.1 @**Prespecifications.**

There were several pre-specified primary efficacy endpoints. There was no specification of whether one or the other CLZ doses was to be compared to placebo in a primary analysis. Additionally, both ICD and ACD were included as goals of primary analysis. One set of these endpoints evaluated the percent change from pre-treatment (baseline) walking distance at the last observation, expressing the central tendency of log-transformed data in terms of the geometric mean[4] and calculating the logarithms of the ratios of final distance/pre-treatment distance, while employing an all-randomized and intent-to-treat (ITT) dataset in which missing data were to be

[3] ankle brachial indices were calculated by a modification of the method of Rutherford.

[4] efined as the *n*th root of the product of *n* observations, the geometric mean is the antilog of the mean of the log values. The logarithm of the geometric mean is equal to the mean of the logarithms of the observations. For example, when the number of observations equals two, the geometric mean equals the square root of the product of the two observations.

handled by the last observation carry foward (LOCF)[5] method; one of these endpoints focused on ICD and the other on ACD.

One other set of these primary endpoints involved a vaguely described group comparison of median ICD and ACD (no analysis of this appears to have been submitted).

Prespecified secondary efficacy endpoints called for many additional methods of assessing walking distances, including:
- Kruskal-Wallis tests on ranks of log (final distance/pre-treatment distance);
- categorical analysis (using the Cochran-Mantel-Haenszel test) of the percent change from pre-treatment ACD and ICD at each time point, grouped into the categories: 0% or less, 1- 50%, 51-100%, and 4) > 100%.
- analysis of variance comparing log (final distance/pre-treatment distance) [this was abandoned because normality assumptions were not met].
- logrank scores compared using the extended Mantel-Haenszel procedure [this analysis was also reportedly not performed; the sponsor states that " it was deemed unnecessary to the analysis"].
- quality of life (QOL) assessment by the Walking Impairment Questionnaire (WIQ)[6], the Medical Outcomes Scale Short Form 36 (SF-36)[7], and by an instrument (known as the Claudication Outcome Measures (COM)) which has reportedly not ungone any assessment of validity.

The prespecified primary safety endpoint was the assessment of a combined morbidity/mortality endpoint using standard life table analyses, with adjustment for covariates using the proportional hazards model. This endpoint will be discussed in detail in the Safety section of this review ("Pooled Composite Endpoint" subsection). In brief, its components were:
- all-cause death
- myocardial infarction (MI).
- stroke: defined as neurological deficit ≥ 24 hours and confirmed by angiography, computed tomography, or magnetic resonance imaging.
- arterial revascularization: angioplasty or vascular reconstruction.
- amputation for worsening arterial status.

Other safety endpoints included: 12-lead EKG, adverse event (AE) assessment, vital signs, serum chemistry, hematology (all assessed prior to treatment and every 2 weeks post-randomization during the first 2 months, then monthly thereafter), and urinalysis (assessed monthly).

---

[5] in the two circumstances in which the last nonmissing value cannot be imputed (i.e. where all preceding observations were missing, or where only the first observation was nonmissing) the subject is excluded from LOCF analyses.

[6] validation of the WIQ instrument was assessed by Regensteiner et. al. in J Vasc Me Biol 2:142-151; 1990.

[7] validation of the SF-36 instrument was assessed by J. Ware in a 1993 document entitled "SF-36 Health Survey: Manual and Interpretation Guide".

Blood samples were obtained prior to treatment and every 2 weeks post-randomization during the first 2 months, then monthly thereafter. To maintain the blind, plasma drug concentrations were t provided to the sponsor until the database lock.

In a substudy patients also underwent 48-hour Holter monitoring prior to and 12 weeks after treatment.

8.1.5.2 **@Measurement methods** (study 21-92-202)

The "immediate-incline" treadmill method was used wherein the incline load started immediately at 12.5% (and remained constant), with speed also constant at 3.2 km/h (2 mph). Walking tests were only to be stopped for claudication of sufficient severity to cause the subject to be unable to continue walking. There was no prespecified provision for tests to stop for such reasons as reaching an arbitrarily long duration or distance of walking.
Attempts were to be made to use the same treadmill and same technician for each test. The treadmill and timer were calibrated within 6 months of testing.

Doppler-estimated supine systolic BPs were obtained prior to tests, and at 1, 5, and 9 minutes post-walking. The three quality of life questionnaires (the COM, WIQ, and SF-36) were administered as telephone interviews. Blood samples were assayed using HPLC for ncentrations of cilostazol and its two main metabolites (OPC-13213 and OPC-13015).

8.1.6 **@Statistical analyses.** (study 21-92-202)

It was prespecified that analyses were to be based on two-sided testing at an alpha level of 0.05.

Geometric mean changes were converted to geometric mean percent change by the following calculation: Geometric Mean % Change = [(Geometric Mean) - 1] x 100.

The Kruskall-Wallis test was done first, and when it showed significance the Wilcoxon rank sum test was used for pairwise comparisons. The pairwise p-values were not interpreted unless the overall treatment test was significant ($p \leq 0.05$), but these pairwise comparisons were not adjusted for multiple comparisons.

Data from demographic and pre-treatment measurements were analyzed for comparability across treatment groups using the Kruskal-Wallis test for continuous variables and Cochran-Mantel-Haenszel test for categorical variables.

For assessment of morbidity/mortality status, an attempt was to be made to capture outcome in ncompleters by making telephone or other contact every 30 days post-termination up to 24 weeks postrandomization or until patient death.

The secondary outcome variable of "cardiovascular morbidity/mortality" was used to determine sample size. A 10% composite event rate was assumed for placebo patients over a 24-week treatment period. The sponsor reports that the sample size required for 80% power of detecting a doubling of this event rate, at a two-sided alpha level of 0.05, was 428. It is not clear what assumptions were made about the rate of subject attrition.

For physician and patient assessments, only observed cases were analyzed (i.e. missing data were excluded).

For Quality of life assessments, only observed cases were analyzed (i.e. missing data were excluded). Repeated measures ANOVA was used to assess the overall change in each subscale contained in the quality of life and patient questionnaire scales over time. The model incorporated as repeated measures the questionnaires at pretreatment and weeks 4, 8, 16, 20, and 24. In addition, the Kruskal-Wallis test and Wilcoxon rank sum test were used to analyze change in each subscale at weeks 4, 8, 16, 20, and 24.

The sponsor reports that there was no interim look for this study.

A blinded, independent Executive Committee convened twice to adjudicate morbidity and mortality endpoints. Their diagnoses were final.

8.1.7 @**Results other than Efficacy outcomes** (study 21-92-202)

8.1.7.1 @**Code breaks**:

The reported code breaks were not of sufficient quality and/or quantity to plausibly influence outcome measures. The blind was reportedly broken for three patients (subject146 unblinded on12/15/93, subject236 unblinded on 12/14/93 and subject305 unblinded on 12/21/93) reportedly due to severe toxicity.

8.1.7.2 @**Covariates**: (study 21-92-202)

Demographic and pre-treatment characteristics of the 419 subjects with post-randomization walking test data are shown in the table below. There were no statistically significant between-group differences in these covariates. Prior to treatment the cilostazol-randomized groups tended towards more severe claudication (i.e. 6-18 meter lesser walking distances) than did the placebo group, but these were reportedly not statistically significant differences. There were no statistically significant between-group differences in duration of peripheral vascular disease diagnosis, or in frequencies of prior revascularizations (femoral-popliteal bypass, angioplasty, or endarterectomy).