**Marketing Exclusivity**

Under sections 505(c)(3)(D)(ii) and 505(j)(4)(D)(ii), Otsuka America Pharmaceutical, Inc. (OAPI) claims 5 years exclusivity from the date of approval for Pletal® tablets (cilostazol) for the indication of intermittent claudication secondary to chronic occlusive arterial disease.

OAPI is entitled to this exclusivity because this new drug application contains the following new investigations which were conducted and sponsored by OAPI and which are essential to the approval of the application:

**Report 21-90-201:** A Randomized Double-Blind Placebo Controlled Study of Cilostazol (OPC-13013) in Patients with Intermittent Claudication Secondary to Chronic Occlusive Arterial Disease.

**Report 21-93-201:** A Randomized Double-blind Placebo Controlled Study of the Effect of Cilostazol in Patient with Intermittent Claudication Secondary to Peripheral Vascular Disease on Walking Distances and Plasma Lipids.

**Report 21-94-201:** A Randomized Double-Blind Study of the Effect of Cilostazol Versus Placebo on Walking Distances in Patients with Intermittent Claudication Secondary to Peripheral Vascular Disease.

**Report 21-92-202:** A Randomized Double-Blind Placebo Controlled Multidose Study of Cilostazol in Patients with Intermittent Claudication Secondary to Chronic Occlusive Arterial Disease.

**Report 21-94-203:** A Randomized, Double-Blind Placebo Controlled Study of the Effect of Cilostazol on Walking Distances in Patients with Intermittent Claudication Secondary to Peripheral Vascular Disease.

**Report 21-95-201:** A Randomized Double-Blind Study of the Safety and Efficacy of Two Different Doses of Cilostazol versus Placebo in Patients with Intermittent Claudication Secondary to Peripheral Vascular Disease.

These clinical investigations are "new" in that they have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of any such investigations.

These investigations were "conducted or sponsored by Otsuka" in that Otsuka America Pharmaceutical, Inc., was the sponsor of the investigational new drug application under which the investigations essential to approval of the application were conducted.

**PEDIATRIC PAGE**

(Complete for all original applications and all efficacy supplements)

**NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.**

NDA/BLA # 20-863 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-110 Trade and generic names/dosage form: Pletal (cilostazol) Action: AP AE NA

Applicant Otsuka America Therapeutic Class 15

Indication(s) previously approved NA

Pediatric information in labeling of approved indication(s) is adequate X inadequate __

Proposed indication in this application Intermittent claudication

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

**IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS?** ___Yes (Continue with questions) ___No (Sign and return the form)

**WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED?** (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 4. X **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed. INFREQUENT IN CHILDREN. NO SINGLE disease entity which corresponds to the adult disease. There may be some patients whose exercise is limited by vascular dis. This was not studied in adults. As the

___ 5. **If none of the above apply,** attach an explanation, as necessary.

**ARE THERE ANY PEDIATRIC PHASE 4 COMMITMENTS IN THE ACTION LETTER?** ___ Yes X No
**ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.**

This page was completed based on information from Medical Group Leader (e.g., medical review, medical officer, team leader)

Gary Buehler Project Manager — 7/13/98

Signature of Preparer and Title — Date

cc: Orig NDA/~~BLA~~ # 20-863
HFD-110 /Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)**

## Debarment Certification

Pursuant to section 306(a) and (b) of the Federal Food and Drug, and Cosmetic Act [21 USC 335(a) and (b)], Otsuka America Pharmaceutical, Inc. (OAPI) certifies that no one who has been employed or is currently employed by OAPI or who was contracted in connection with the cilostazol NDA has been debarred. Additionally, we certify that there are no debarment procedures pending for any current or past employee of OAPI or its contractors who participated in the development of cilostazol. Our conclusions regarding debarment status were reached by comparing the current FDA debarment list (Dated: April 2, 1996) to the listing of past and present OAPI employees and to certifications obtained from our contractors.

David H. Warnock

August 21, 1997

David Warnock, Ph.D.
Director, Regulatory Affairs
Otsuka America Pharmaceutical, Inc.
2440 Research Boulevard
Rockville, MD 20850

Date

G. Mueller FEB 2 3 1998

(895)

# REQUEST FOR TRADEMARK REVIEW

TO: CDER Labeling and Nomenclature Committee
Attention: Dan Boring, R.Ph., Ph.D. HFD-530
9201 Corporate Blvd. Rm N 461

FROM: Division of: Cardio-Renal Drug Products HFD-110
Attention: Robert Wolters Phone: 594-5376

DATE: October 21, 1997

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Proprietary Name: Pletal NDA/ANDA 20-863

Trademark status: Yes

Company Name: Otsuka

Other proprietary names by the same firm for companion products:
None

Established name including dosage form and strength:
Cilostazol 50 & 100 mg tablets

Indications for use including dosing schedule (may be a summary if proposed statement is lengthy):
Chronic Occlusive Arterial Disease

Comments from the submitter: (concerns, observations, etc.)

This trademark was sent to the L&N Committee last March and found acceptable. See consult # 778

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. Dec.96

Consult #885 (HFD-110)

PLETAL cilostazol tablets

The Committee noted sound-alike/look-alike conflicts with the following marketed products: PLENDIL and PLATINOL. The committee felt there was a low potential for mix-up with these products since they are different dosage forms (PLATINOL), strengths and therapeutic classes. There were no misleading aspects found.

The Committee has no reason to find the proposed proprietary name unacceptable.

P Uberuaga 2/18/98, Chair
CDER Labeling and Nomenclature Committee

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: SEP 18 1998

FROM: Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: NDA 20-863, cilostazol (Pletal), Otsuka America Pharmaceutical, Inc.
For the treatment of intermittent claudication

TO: Director, Office of Drug Evaluation I, HFD-101

**Introduction**

Writing this memorandum has been a bittersweet job. On the one hand this NDA contains clear-cut (more clear-cut than I have ever seen for almost anything) proof of symptomatic benefit in patients with intermittent claudication. On the other hand, a development program that was conceived in the mid-1980s, being mainly executed between 1991 and 1997, did not anticipate nor provide data to confront bias materially that positive inotropic agents that increase myocardial cyclic AMP have a detrimental effect on mortality when administered chronically to patients with congestive heart failure.

In January 1998, the Cardiovascular and Renal Drugs Advisory Committee met to discuss the role of inotropes in heart failure. This meeting led to labeling that, in part, reads as follows:

> *. . . In controlled trials of chronic oral therapy with various such agents . . . the cyclic-AMP-dependent inotropes were consistently associated with increased risks of hospitalizations and death. Patients with NYHA Class IV symptoms appeared to be at particular risk . . ..*

Additionally, because of the ability of cilostazol to inhibit platelet aggregation, the cilostazol-controlled protocols (not entirely successfully) excluded concomitant use of any other drug that inhibited platelet aggregation. It was not known at the time of the cilostazol trials (ending of the last study was in 1997) that in 1998, clopidogrel would be approved for use in patients with peripheral arterial disease because of favorable effects upon mortality. There is at present some but no extensive clinical trial experience with cilostazol in combination with anti-platelet aggregation agents.

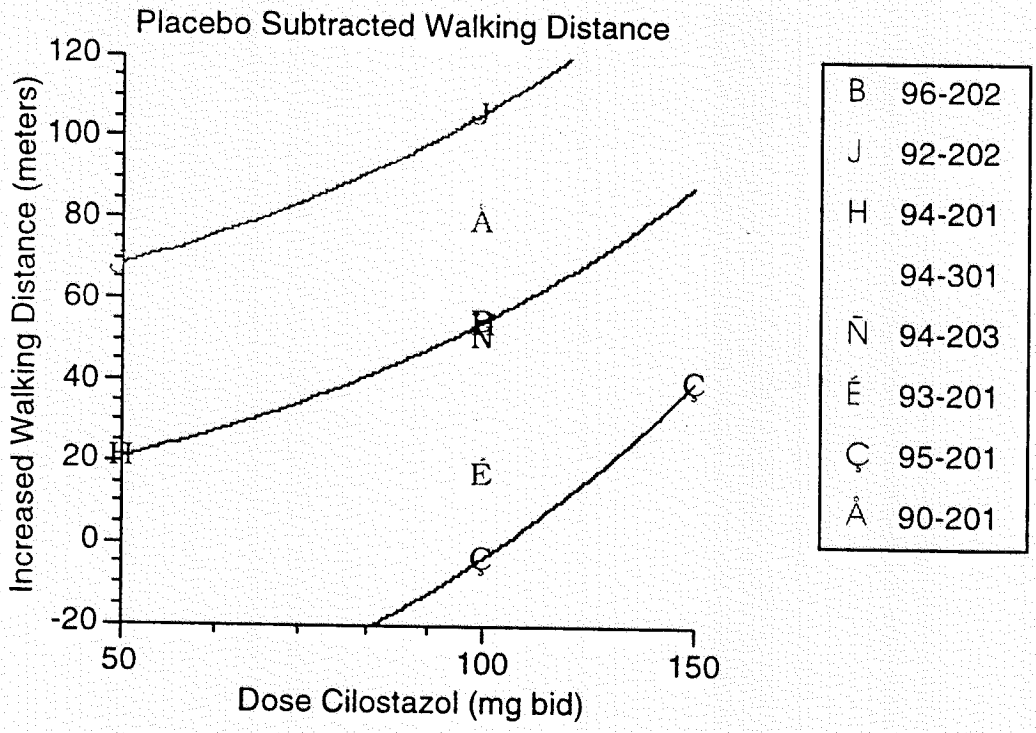
**Placebo-Controlled Efficacy Trials**

Exercise Tolerance Testing. Throughout the documentation (Medical and Statistical reviews) the 8 randomized, placebo-controlled trials that were conducted and support the approvability of cilostazol are summarized (representing 2703 randomized patients). The major endpoint of these trials was symptom limited exercise tolerance tests (ETT); intermittent claudication was the limitation for randomization, any symptom was the limitation following randomization. Major statistical testing was by intent to treat with last observation carried forward. Peak and trough ETTs were conducted. At no time, in any trial was a point estimate for cilostazol mean ETT inferior to that of placebo. Of the 11 cilostazol comparisons to placebo, 3 had 95% confidence limits that included no effect of cilostazol with other comparisons having p values ranging from 0.001 to 0.0309 with 6 of those 11 being less than 0.002. Patients receiving cilostazol were certainly able to exercise longer than those receiving placebo.

"Quality of Life." A number of standard "quality of life" (standard to investigators that work in this area) were used in 6 of the controlled trials. Those elements of the instruments used that dealt with the physical component of living, gave results in qualitative agreement with the above ETT results. Of the 6, none had cilostazol point estimates inferior to placebo and 4 of the 6 were statistically significantly better than placebo ($p < 0.05$).

Patient Population Studied. The patient population enrolled in trials, namely, those with stable intermittent claudication, represent about 30% of patients with peripheral vascular disease (50% of the general population with peripheral vascular disease being asymptomatic; the other 20% having progressive limb compromise, not just stable claudication). About 60% of the population studied had concomitant hypertension, 30% concomitant diabetes, 28% having had a myocardial infarction, 20% having a history of angina (but that was not their exercise symptom limitation at the time of randomization), and between 5 and 15 % having had a stroke, congestive heart failure, a TIA or cardiac arrhythmias. Consequently, patients enrolled in trials were concomitantly receiving many other medications that included most of the major classes of drugs used in cardiovascular therapy (32 different classes of drugs).

Dose Response (ETT)




The above figure shows placebo subtracted change (of the means for each group) from baseline for each of the 8 trials as a function of dose. A few obvious things, I think, can be seen. The dose range explored was only a factor of 3 (50 to 150 mg bid), with only one trial (trial 95-201, 53 patients) receiving 150 mg bid. Each of the trials that explored more than one dose, had the greatest dose having the greatest effect (I have not calculated the p value, but I think this shows a definite dose-related effect; the triangle at 100 mg for trial 940201 is hidden by the square for trial 96-202). Absolute meters increase is pretty variable (in part dependent upon sample size). The weighed, pooled mean treatment effect for all 8 trials at 100 mg bid being 63 meters (somewhere in the neighborhood of one city block). Note for trial 95-201, the 100 mg dose had a negative point estimate (but above I stated that there were no negative treatment effects). Both assertions are correct. What is plotted is change from baseline based on adjusted data (least square mean). The principal group was on estimated treatment effect as a ratio of geometric mean which

in the 100 mg, 90-201 group turned out to be 1.02 (1.00 being no difference). The 100 mg dose for trial 90-201 turned out to be not statistically significantly different from placebo (p=0.7925); quite clearly. I think, an anomalous finding.

Adverse Effects. Adverse effects clearly related to cilostazol (because of an increased frequency, compared to placebo) were headache (an incidence of about 19 to 26% greater than that of placebo), palpitation (an incidence of about 8 to 13% greater than that of placebo), abnormal stools (an incidence of about 11% greater than that of placebo), diarrhea (an incidence of aobut 12 to 14% greater than that of placebo), and dizziness (an incidence of about 8% greater than that of placebo). Each of these apparently increasing in incidence as dose increased.

**Two (of the 8) Trials Placebo/cilostazol/pentoxifylline**

Both of these trials have been submitted and have been reviewed. Each of them, 94-301 and 96-202, are summarized above as 2 of the 8 placebo comparisons. Each trial compared 100 mg cilostazol, bid, to pentoxifylline 400 mg tid and to placebo, in multicenter, randomized, controlled trials.

Trial 96-202 randomized 643 patients (205 to cilostazol, 212 to pentoxifylline, and 226 to placebo) for 24 weeks of double-blind therapy. Cilostazol was superior to placebo (p=0.0005) and to pentoxifylline (p=0.0002), pentoxifylline was not superior to placebo (p-0.8190).

Trial 94-301 randomized 363 patients (123 to cilostazol, 118 to pentoxifylline, 122 to placebo) for 24 weeks of double-blind therapy. In this trial, none of the 3 groups were found to be statistically significantly different from one another at any week of the 24 week trial. Mean point estimates ordered with pentoxifylline being better than placebo and cilostazol being better than pentoxifylline; but none were statistically significantly different. Qualitatively, 94-301 showed results like those of 96-202, but the treatment effects were smaller and the variance a little larger.

In any event, the data do not support a direct comparative claim.

**The Hard Part**

Phosphodiesterase Inhibition. Cilostazol is a relatively specific inhibitor of phosphodiesterase III (myocardial phosphodiesterase [PDE]); the $IC_{50}$ (in micromoles) is 0.19, 14 and 96 for PDE-III, PDE-V and PDE-II, respectively, PDE isolated from human platelets; so about 3 orders of magnitude more potent for PDE-III. In PDE isolated from dog aorta, the $IC_{50}$ as 0.44, 59 and >100 for PDE-III, PDE-II and PDE-I, respectively.

Associated with the PDE-III activity, cAMP levels are increased in a dose dependent fashion. Cilostazol also lowers peripheral resistance and increases femoral blood flow in animal models. So, it has the basic pharmacological properties of an inotrope vasodilator, like amrinone.

Like other drugs that have these properties, cilostazol produces subacute animal toxicology that (among other things) is characterized by subendocardial myocardial necrosis and hemorrhage. It is not possible to distinguish cilostazol qualitatively from any of the other inotrope vasodilators that are characterized by PDE-III inhibition/ intracellular cAMP increase, and increased mortality when used chronically in the treatment of patients with congestive heart failure.

Of the 2473 patients randomized to placebo (1032) or cilostazol (1441), there were 19 deaths (7 in the placebo groups, 12 in the cilostazol groups). So, the point estimate (with very wide confidence limits) is in a direction that supports the negative inotrope/vasodilator bias. Mortality in the population studied was between 0.68 and 0.83%), which from what can be gleaned from the literature for persons with stable claudication is about the right incidence. So, to gain sufficient numbers of events in this population to make meaningful statements would require sample sizes in the 10s of thousands.

Not comforting is the occurrence of palpitations (apparently dose-related), as was a small increase in heart rate, and from a total of 260 patients (180 cilostazol, 80 placebo) that had holters one could argue that a pro-arrhythmic effect was found. Although not definitive, consistent with a worry about the possibility of an increase in mortality that might be related to cilostazol treatment.

Data do not exist that will allow a data dependent judgement to be made. The Advisory Committee was comfortable with approving cilostazol, provided that the patients who would be taking cilostazol were made aware of the ambiguity related to morbidity/mortality. The Division concurs with the Advisory Committee's advice.

**Recommendations**

The Division recommends that cilostazol be approved for the treatment of intermittent claudication. Labeling should include a patient package insert that describes the uncertainty related to long term mortal/morbid events, but also clearly state the symptomatic improvement that is a certainty.

**Post-Marketing Activity**

In the meantime, the package insert can contain precaution against concomitant use of anti-aggregating agents, as well as against concomitant use of CYP3A4 and CYP2C19 metabolized drugs. The sponsor will have some specific drug interaction studies with kovastatin and clopidogrel concluded by the end of October 1998. Protocols have been submitted, reviewed by Dr. Marroum and found to be acceptable. Labeling may be changed by those results.

The firm was informed that they did not have to submit a final safety update.

A marked-up package insert, a marked-up draft patient package insert and an approvable letter are appended.

cc
Orig.
HFD-110
HFD-110/G Buehler
HFD-110/R Lipicky
sb/8/4/98;8/14/98
R/D: G Buehler
N Morgenstern

Buehler
JUL 23 1998

Table of Contents



Abraham Karkowsky, M.D. Ph.D.
22 July 1998

cc: NDA 20-863; File
HFD-110: AKarkowsky, SRodin,
HFD-710; KMahjoob; KJin ; LCui

1. Preamble:

The initial NDA for cilostazol was delivered to this Division on 19 September 1997. The initial submission contained reports of all the clinical studies with the exception of the pentoxifylline comparisons studies #21-96-202 and #21-94-201. These last studies were submitted on 29 may and 1 June 1998. Dr. Steve Rodin, the medical officer was responsible for the Medical review of all the pivotal studies as well as the human safety. Dr. Karkowsky reviewed the sundry clinical pharmacology studies. Dr. Kun Jin completed the statistical analysis of the six largest placebo-controlled studies; Dr. Kooros Mahjoob and Dr Lin Cui each reviewed the statistics of one of the pentoxifylline-controlled studies. Dr. John Koerner reviewed the pre-clinical pharmacology and Dr Xavier Joseph the toxicology, carcinogenicity, mutagenicity and teratology. Dr. Venkata Ramana S. Uppoor, reviewed the biopharmaceutical studies, Dr. El Tahtawy performed the population PK analysis. Dr. Jim Short reviewed the Chemistry.

This review, in DRAFT, was supplied to the Cardio Renal Advisory Committee (CRAC) prior to their deliberation on 9 July 1998. Since both Dr. Temple and Dr. Lipicky were present at the CRAC deliberations, no recommendations will be included at the end of this review.

The pivotal clinical studies explored the ability of cilostazol to increase exercise performance among patients with intermittent claudication. None of the studies enrolled extremely compromised patients. There is, therefore, no information about the effect of cilostazol in either preventing either limb loss or delaying the need for revascularization procedures.

Introduction:

Cilostazol (Pletal®), OPC-13013), is chemically 6-[4-(1-Cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydrocarbostyril (CAS-73963-72-1; see Figure 1 for cilostazol's structure). The drug has no optically active centers. Some of the metabolites of cilostazol, however, result from the oxidation of the cyclohexyl ring. The resultant hydroxyl-group could either be cis or trans to the tetrazol group. In addition, there is the potential for optical isomerization of the resultant oxidized product. Each product, however, is designated by a unique OPC-number.

Cilostazol is a Type III phosphodiesterase inhibitor which inhibits cAMP degradation and consequently increases the intracellular concentration of cAMP. The consequence of elevated cAMP levels include: vascular dilation, cardiac inotropy, airway dilation stimulation of lipolysis and inhibition of platelet aggregation.

Several Type-III PDE inhibitors, such as milrinone, amrinone and enoximone have been explored as clinically useful agents, for the treatment of congestive heart

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failure. Except for milrinone, which is approved for short term intravenous treatment of congestive heart failure, none of the other drugs are approved. Flosequinan, though a non-specific PDE inhibitor, is an inotrope/vasodilator was approved for symptomatic treatment of CHF. Flosequinan, however, was approved withdrawn by its sponsor from market, because of an adverse mortality effect and evidence of diminishing symptomatic benefit.

Long term use of several of the PDE-Type III drugs have generally demonstrated a negative survival outcome for congestive heart failure patients (milrinone[1], enoximone[2], pimobendan[3], vesnarinone[4] and flosequinan[5]). None of these drugs, however, were explored as treatments for intermittent claudication.

The theoretical basis for using the PDE-III inhibitor, cilostazol, to treat intermittent claudication rests on its vasodilating and platelet anti-aggregatory actions. Presumably, these actions are able to increase blood flow at sites distal to the point of claudication.

Animal Pharmacology:

Cilostazol is able to inhibit PDE-III in both human (platelets, and umbilical vein endothelium)[6] and dog (aorta[7], femoral artery, cardiac muscle[8]) . The concentrations of cilostazol which produced $IC_{50}$ for inhibiting PDE-III enzymatic

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[1]Packer, M.; Carver, J.R.; et al.; "Effect of Oral Milrinone on Mortality in Severe Chronic Heart Failure"; N Engl J Med 1991; 325: 1468-75.

[2]Cowley, A.J.; Skene, A.M.; "Treatment of Severe Heart Failure : Quantity or Quality of Life? A Trial of Enoximone". Br Heart J 1994; 72:226-230

[3]Pimobendan in Congestive Hert Failure (PICO) Investigators; "Effect of Pimobendan on Exercise Capacity yi Patient with Heart Filure: Main Results from the Pimobendan in Congestive Heart Failure (PICO) Trial" Heart ;1996; 76: 223-231.

[4]Feldman, A.; Young, J. Et al.; "Mechanism of Increased Mortality From Vesnarinone in the Severe Heart Failure Trial (VesT)". J Amer Coll Cardiol. 1997; 29: 64A.

[5]Packer, M.; Rouleau, J.; et al.; "Effect of Flosequinan on Survival in Chronic Heart Failure: Preliminary Results of the Profile Study. Circulation 1993; 88 (Suppl I) I-301.

[6]Report # 005272, Study number not given.

[7]Study #012137

[8]Study #006435