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Joan Claybrook, President

December 30, 1998

Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Woodcock:

On September 18th of this year, we wrote you (see enclosed copy) strongly urging that the FDA not approve the drug cilostazol (Otsuka) for treatment of intermittent claudication (leg pain on exercise in people with inadequate arterial blood flow to their legs) due to very worrisome heart problems caused by the drug. Three members of the FDA's Cardiovascular and Renal Advisory committee voted against approving the drug due to these safety problems which were evident in the studies presented to that committee on July 9, 1998. These included abnormal electrocardiograms, increased heart rate, increased ventricular arrhythmias (premature ventricular contractions) and a suggestion, though not statistically significant, of increased mortality, even though the longest time studied on the drug was just six months. A recent study (see below) on a related drug, not available at the time of the advisory committee meeting, has amplified our concerns about the safety of cilostazol and prompted this letter.

As you know, cilostazol is in a class of drugs called phosphodiesterase inhibitors which inhibit the enzyme which otherwise breaks down cyclic AMP (cAMP), resulting in higher tissue levels of cAMP. Cilostazol inhibits phosphodiesterase III (PDE III), platelet activation and causes blood vessel-relaxation.

A study, published two weeks ago in the *New England Journal of Medicine* (December 17, 1998) reported on the increased death rate in people using vesnarinone, also a phosphodiesterase III inhibitor, for the treatment of heart failure. According to the authors, "The increase in mortality with vesnarinone was attributed to an increase in sudden death, presumed to be due to arrhythmia." The FDA wisely averted a disaster by not approving vesnarinone (also an Otsuka drug) and, instead, asked for the study which was just published. Vesnarinone is the fifth PDE III inhibitor drug, all used to treat heart failure, found to cause increased mortality (See table below which reviews data on four of these drugs; the fifth is amrinone for which such data are not available). Pimobendan was never approved in the US; flosequinan was taken off the market here because of heart toxicity and amrinone and milrinone have only limited, short-term injectable use in this country because of their dangers.

PHOSPHODIESTERASE III INHIBITORS FOUND TO INCREASE MORTALITY IN RANDOMIZED CONTROLLED CLINICAL TRIALS		
Drug	Active Treatment Group Deaths, Events (%)	Placebo Group Deaths, Events (%)
Flosequinan.[1] This study ran for its planned duration of 16 weeks. (Another study, The Prospective Randomized Flosequinan Longevity Evaluation, or PROFILE trial was terminated because of an adverse effect on mortality; no data are available from this trial).		
	All deaths 75 mg = 5 (**4.9%**)	6 (**5.5%**)
	All deaths 100 mg = 8 (**7.3%**)	6 (**5.5%**)
Milrinone.[2] This trial was stopped after 22 months.		
	Cardiovasc. deaths = 165 (**29.4%**)	119 (**22.6%**)
	All deaths = 168 (**30%**)	127 (**24%**)
Vesnarinone.[3] This study was stopped after 20 months.		
	Cardiovasc. deaths 30 mg = 248 (**19.5%**)	231 (**18.0%**)
	Cardiovasc. deaths 60 mg = 271 (**21.3%**)	231 (**18.0%**)
	All deaths = 292 (**22.9%**)	242 (**18.9%**)
Pimobendan.[4] This study ran for its planned duration of 12 weeks.		
	Cardiovascular deaths 2.5 mg = 0 (**0%**)	3 (**6.1%**)
	Cardiovascular deaths 5 mg = 3 (**5.8%**)	3 (**6.1%**)
	Cardiovascular deaths 10 mg = 5 (**10.2%**)	3 (**6.1%**)

[1] Massie BM, Berk MR, Brozena SC, et al. Can further benefit be achieved by adding flosequinan to patients with congestive heart failure who remain symptomatic on diuretic, digoxin, and an Angiotensin Converting Enzyme Inhibitor? Circulation 1993;88:492-501.

[2] Packer M, Carver JR, Robeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. New England Journal of Medicine 1991;325:1468-1475.

[3] Cohn JN, Goldstein SO, Greenberg BH, et al. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. New England Journal of Medicine 1998;339:1810-1816.

[4] Kubo SH, Gollub S, Bourge R, et al. Beneficial effects of pimobendan on exercise tolerance and quality of life in patients with heart failure. Circulation 1992;85:942-949.

It is of special concern that although patients with significant heart failure were excluded from the clinical studies on cilostazol and the use in such patients would be contraindicated, many patients with intermittent claudication also have actual or incipient heart failure and are likely to be prescribed the drug by their physicians. Given the absence of reliable long-term data on the risk of death caused by the drug and the clear evidence of increased death in the other five drugs in this class in people with heart failure, it is inevitable that many people with heart failure will use cilostazol, and, in many cases, will die from the drug.

It is less than a year since mibefradil (Posicor), a drug for high blood pressure, was banned after causing a large number of cardiac deaths. The FDA missed an opportunity to avoid this disaster. Before the approval of mibefradil, one of the members of the FDA advisory committee who voted against cilostazol (Dr. Lemuel Moye, U. Texas School of Public Health, Houston) warned the FDA not to approve mibefradil. because of the deaths it might cause. In part, his concern was of abnormal electrocardiograms and the interim results of a mibefradil study on patients with heart failure showing increased death rates in those taking the drug, although the findings were not statistically significant. His concerns were extremely prescient and, we believe, right again in the case of cilostazol. As with mibefradil, there is concern about the use of cilostazol with other drugs such as platelet-inhibiting drugs which may produce harmful interactions such as bleeding.

Too many recently-approved drugs have already had to be taken off the market because they were too dangerous or, like the diabetes drug Rezulin, will soon have to come off the market. We strongly urge you not to make yet another mistake with cilostazol. Although the FDA has apparently said the drug is "approvable" it should not be approved. We said this when we wrote to you in September and the evidence is even stronger now.

Sincerely,

Sidney M. Wolfe, M.D., Director

Larry D. Sasich, Pharm. D., MPH, Staff Researcher

Elizabeth Barbehenn, Ph. D.
Pharmacologist

Public Citizen's Health Research Group

STATEMENT BY SIDNEY M. WOLFE, M.D. AND LARRY D. SASICH, PHARM.D, M.P.H. OF PUBLIC CITIZEN'S HEALTH GROUP
ON THE EFFECTIVENESS OF CILOSTAZOL (PLETAL) COMPARED TO PENTOXIFYLLINE (TRENTAL)
AND THE ESTABLISHED EFFECTIVENESS OF EXERCISE
December 31, 1998

Pentoxifylline (Trental) is the only drug currently approved in the U.S. for the treatment of intermittent claudication, which is defined as a pain, ache, cramp, numbness, or sense of fatigue in the muscles that occurs during exercise but is relieved with rest.

According to information presented by Otsuka America (sponsor of the cilostazol application) at the July 9, 1998 advisory committee meeting, contained in the slide attached to this statement, pentoxifylline is only "minimally effective" in the treatment of intermittent claudication. Yet, the FDA advisory committee determined that the company's claimed advantage of cilostazol over pentoxifylline was inconclusive. The members of the FDA's Cardiovascular and Renal Drug Advisory Committee were asked at this meeting:

> Which (if any) of the trials showed that cilostazol is superior to pentoxifylline for the claimed indication. If there are trials in each category, is that a problem?[1]

"The committee voted 10 to zero that the data are inconclusive" regarding the superiority of cilostazol over pentoxifylline.[2] Therefore, using the company's assessment of pentoxifylline (with which we agree) as "minimally effective" and the FDA advisory committee's assessment of cilostazol as not being conclusively superior to pentoxiphylline, it is reasonable to conclude that cilostazol is only minimally effective as well.

That there is an effective alternative is admitted by Otsuka in the same slide in which supervised exercise is described as "very effective". The effectiveness of exercise alone can be seen in the data from the clinical trials presented at the FDA advisory committee meeting.

Two clinical trials were conducted that compared cilostazol 100 mg twice daily, pentoxifylline 400 mg three times a day, and an inactive placebo for this condition. The efficacy of cilostazol was assessed by the absolute claudication distance or ACD. The

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[1] Question 6 for the advisory committee from the Food and Drug Administration, July 9, 1998.

[2] Transcript of the Food and Drug Administrations's Cardiovascular and Renal Drugs Advisory committee Meeting, Thursday, July 9, 1998, page 355.

ACD is the maximal distance the patients can walk on a treadmill.[3]

Study 96-202 involving 516 patients conducted in the U.S. found that cilostazol 100 mg increased walking distance 66 percent more than pentoxifylline or placebo. The effect of pentoxifylline was virtually indistinguishable from the inactive placebo. The result was statistically significant (p=0.0002). At the end of the study, the maximal walking distance in cilostazol treated patients increased 113 meters while it increase 68 meters in placebo and pentoxifylline treated patients.[4] This difference is 45 meters or about 147 feet which is less than 50 yards.

Study 93-301 conducted in the United Kingdom involved 370 patients and did not find a statistically significant difference between cilostazol and pentoxifylline. Patients receiving cilostazol were able to walk 33 meters further than those taking the placebo at the end of the study.[2] This difference of 33 meters is about 108 feet or 36 yards.

Both of these trials lasted 24 weeks and at the end of this period of time patients taking cilostazol could walk between 36 and 50 yards farther than those taking pentoxifylline.

Clearly, given that cilostazol is at best only minimally effective (beyond exercise) and given that supervised exercise is very effective and much safer than cilostazol, health care resources should be directed toward increasing the availability of supervised exercise for patients with intermittent claudication rather than paying for minimally effective and probably dangerous drugs.

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[3] Transcript of the Food and Drug Administrations's Cardiovascular and Renal Drugs Advisory committee Meeting, Thursday, July 9, 1998. The complete transcript of this meeting can be found on the FDA's web site at www.fda.gov/ohrms/dockets/ac/98tctm.htm#Center for Drug Evaluation and Research (CDER).

[4] Slides presented by Otsuka America Pharmaceuticals, Inc. at the Food and Drug Administrations's Cardiovascular and Renal Drugs Advisory committee Meeting, Thursday, July 9, 1998.

SLIDE PRESENTED BY OTSUKA AMERICA PHARMACEUTICAL INC., AT THE FDA'S CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE MEETING
THURSDAY, JULY 9, 1998

Available Claudication Treatments

	Effectiveness	Limitations
Supervised Exercise	Very	Availability
Unsupervised Exercise	Not	
Angioplasty	Possibly	Morbidity/Mortality
Surgery	Very	Morbidity/Mortality
Pentoxifylline	Minimal	

Circulation 1994;990:1866, Angiology 1997;48:291, J Vasc Surg 1997;26:551
Can Med Assoc 1996;155:1053, JAMA 1995;274:975-980, Ann Surg 1989;209:346

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