#1458

PLETAL

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Joan Claybrook, President

September 18, 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:

We strongly urge you to reject the application for approval of cilostazol (Pletal), a drug to treat intermittent claudication, a chronic, non-life-threatening condition for which there are alternative solutions, including exercise, that do not involve the multitude of known and potentially life-threatening risks that exist with cilostazol. The FDA's Cardiovascular and Renal Advisory Committee voted 7 to 3 to approve the drug on July 9, 1998. However, three members opposed its approval and raised serious questions about its dangers: cardiac effects, concomitant use of other anti-platelet drugs, and mortality. This same advisory committee voted 5 to 3 on February 28, 1997 to approve the now-banned calcium channel blocker mibefradil (Posicor), also over the strong objections of three committee members.

Cilostazol inhibits platelet activation and is a blood vessel-relaxant through inhibition of phosphodiesterase III (PDE III) with a resultant increase in intracellular cAMP; changes in intracellular calcium (as cAMP rises) may be the ultimate cause of these effects. Cilostazol's mechanism of action in improving physical mobility is unknown.

EFFECTS ON THE HEART

Like other PDE III inhibitors, cilostazol increased heart rate, coronary blood flow, and contractility "likely due to elevated intracellular cyclic AMP". Dose-related cardiac changes are shown below:

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TABLE 1 - MEAN CHANGE IN CARDIAC PARAMETERS FROM BASELINE TO END OF TREATMENT				
PARAMETER	Control n=973	50 mg bid n=303	100 mg bid n=998	150 mg bid n=73
PR interval (ms)	0.2	-1.1	-2.8	-5.7
QT interval (ms)	-0.4	-10.8	-14.9	-20.8
Heart rate (bpm)	-0.1	5.1	7.4	10.5
VPBs*/hr (%)	1	5.4	4.3	4.4

*ventricular premature beats

TABLE 2 - TREATMENT-EMERGENT ADVERSE EVENTS (% PATIENTS)				
PARAMETER	Control n=973	50 mg bid n=303	100 mg bid n=998	150 mg bid n=73
Palpitation*	1.0	5.0	9.6	9.6
Tachycardia	0.7	3.6	4.3	9.6
Peripheral edema*	3.8	7.6	6.6	11
Diarrhea*	6.7	11	19	19
Headache*	13	26	33	44

*A certain number of these led to discontinuation of study drug in Phase III trials

CONCOMITANT USE OF OTHER ANTI-PLATELET DRUGS

The FDA advisory panel was asked: Do you need more information on concomitant use of anti-platelet drugs, drugs such as clopidogrel (Plavix) or ticlopidine (Ticlid) because of bleeding? Do you need information on mortality that might result before approving this drug? Note that: "... [any drug] with an anti-platelet activity was excluded" from the cilostazol trials.[1]

> Dr. Moye: "...I am loathe to recommending approval in the absence of information. Information we must have before we make the recommendations. I am uncomfortable with voting for approval for a drug hoping that I am right. I want to be able to vote for approval knowing I am right and I can't know it unless I have seen the authoritative data...it is impossible to vote for approval...we must have the information from the sponsor about the potential interaction here."[2]

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[1]Cardiovascular and Renal Drugs Advisory Committee Transcript; July 9, 1998; p.65

[2]Ibid, p.384.

Dr. Thadani: "Somebody might end up on three anti-platelet agents...I would like to see more data before going ahead and feeling secure that it should be used."[3]

Dr. Graboys: "I don't think we can depend on the labeling and I think we need to have full information before we let this drug loose."[4]

Dr. Grines: "What I do think we need more studies on is a combination of this drug with other vasodilators, which I see as a much bigger potential problem."[5]

One of those anti-platelet drugs that might be given concomitantly and for which we have no information, is ticlopidine, which contains a boxed warning for neutropenia and/or agranulocytosis:

> "The onset of neutropenia may occur suddenly. It is, therefore, essential that CBCs (including platelet count) and white cell differentials be performed every 2 weeks, starting at baseline before treatment is initiated to the end of the third month..."[6]

This warning is for ticlopidine when given alone. What happens when it is added to cilostazol, another anti-platelet drug? An additional question not asked of the committee: What happens when these drugs are combined with Viagra, a PDE V inhibitor, as seems likely to happen, that also has effects on platelet function?

MORTALITY

An analysis by Dr. Rodin, an FDA Medical Officer, showed a "disturbing trend for increasing mortality with increased dose",[7] although it was not statistically significant perhaps because of the short duration of the studies. The 30% increased incidence in mortality was similar to a 28% increase in mortality found with milrinone another, PDE inhibitor. Milrinone and amrinone are both PDE III inhibitors that in long-term studies

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[3]Ibid, p.386.

[4]Ibid, p.387.

[5]Ibid, p.389.

[6]Ticlopidine (Ticlid) Professional Product Labeling. Physicians' Desk Reference 52ed. Montvale, NJ: Medical Economics, Inc., 1998.

[7]Cardiovascular and Renal Drugs Advisory Committee Transcript; July 9, 1998; p.271.

exhibited minimal long-term efficacy and increased mortality in heart failure patients.[8]

PDE drugs were an issue of great concern to the committee: the history of these drugs is such that they are now recommended only for short-term intravenous therapy. There is further reason for concern when one approves a PDE III inhibitor that is to be given with other (anti-platelet) drugs that themselves have a potential for increased morbidity and mortality.

Drs. Moye, Thadani, and DiMarco all felt that a better estimate of mortality was needed.[9]

> Dr. Moye: "We have..a paucity of data post-6 months. And with the concerns that have been raised within the 6-month data base, I just am extremely uncomfortable drawing any conclusion about long-term consequences of exposure..."
>
> Dr. Thadani: "...I would like to see more data on the safety issue that the drug is not going to kill patients over the long run."
>
> Dr. DiMarco: "...the patients I see have heart failure or arrhythmias and angina and, by the way, a little claudication. And I think that is a different population than we are looking at here ...I can't imagine how labeling can keep it from being used in that other population where we have a lot of concerns."[10]

The concerns of the panel were based on the history of "having been burned a lot with these drugs".[11] On the first vote, the committee voted 7 to 3 that they needed more information on mortality before approval. However, they were then asked to assume there would be unit-of-use packaging and that patients would be guaranteed a handout explaining the risks of cilostazol (not a package insert because "nobody [doctors] would read it"). The second vote was 7 to 3 to approve the drug.

We would also urge the FDA to take into consideration the consequences of previous approvals, such as mibefradil, where increased mortality subsequently required the drug to be withdrawn from the market. With cilostazol, we already have an

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[8]Goodman & Gilman's The Pharmacological Basis of Therapeutics; 9th ed. p.833, 1996

[9]Cardiovascular and Renal Drugs Advisory Committee Transcript; July 9, 1998; p.430

[10]Ibid, p.431.

[11]Ibid, p.447.

indication of increased mortality, even when tested in a small, defined population that were not being treated with powerful anti-platelet drugs. Where there exists an alternative therapy with low mortality and where the disease being treated is chronic, but not life-threatening, the drug should be significantly safer than this one appears to be.

Furthermore, the panel noted that patients whose exercise tolerance was limited by heart failure were excluded from this study with the result that we have no information about safety for that patient population. Yet, we know that once a drug is approved, it will certainly be used in this population in which it was never studied. Because the drug was tested in a selected group of patients who did not have severe symptoms, and because testing with patients on additional drugs was limited, there are many potentially serious unknowns with this drug. We request that the FDA wait until a mortality study has been done under conditions that more closely resemble actual clinical use before approving cilostazol.

It must be noted that when mibefradil was being considered for approval, Dr. Moye, of the University of Texas School of Public Health in Houston -- one of the three FDA advisory committee members who opposed its approval -- said that mibefradil should not be approved until the concerns about abnormal electrocardiograms seen in patients receiving the drug that could be lethal were answered. Tragically, as it turned out, he was right and the FDA was wrong in not taking more seriously the strenuous objections of the advisory committee members. With cilostazol, more members might have opposed approval had there not been strong and, it appears to us, highly inappropriate lobbying by both Drs. Raymond Lipicky and Robert Temple. We hope that the FDA does not repeat the same kind of mistake and that cilostazol is not approved until much more is known about its serious dangers.

Sincerely,

ps for E.B.

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ps for S.W.

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