HRG Publication 1385

Statement of Sidney M. Wolfe, M.D
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at FDA Hearing on Calcium Channel Blockers

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On November 9, 1995 Public Citizen's Health Research Group petitioned the FDA to put warning labels on all calcium channel blocker drugs because of the rapidly mounting evidence that a variety of these drugs, used for different medical purposes, including the treatment of hypertension and angina, actually increase rather than decrease the risk of death. The majority of studies including randomized controlled trials and other epidemiological studies either fail to show any clinical benefit, and in many cases actually showed harm to patients using calcium channel blockers.

Our proposed boxed warning label (with a similar one to be required as a patient package insert) is as follows:

Emerging evidence shows a consistent association between the use of the immediate release dosage forms of calcium channel blocking drugs and an increased risk of adverse cardiovascular events including myocardial infarction and death. The evidence to date most strongly implicates the immediate release dosage form of nifedipine in moderate or high doses, but there is no evidence that extended release dosage forms are safer as far as patient mortality is concerned. The three calcium channel blocker sub-types are chemically dissimilar, but they share mechanisms of action. Consequently, it is prudent to consider that this warning should apply to all calcium channel blocking drugs, regardless of chemical class or dosage form (immediate or extended release).

The calcium channel blocking drugs should not be used in those patients with recent myocardial infarction and congestive heart failure.

Drugs from alternative classes of agents for the initial treatment of stable or unstable angina pectoris or hypertension, diuretics and beta-blockers, have reduced major cardiovascular events and mortality in well controlled trials in hypertensive patients. Other agents, including the calcium channel blockers, have not been shown to reduce the incidence of stroke, myocardial infarction or death. Consequently, the Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure recommends diuretics and beta-blockers as the preferred drugs for treating hypertension.

The absence of warnings on these drugs present two public health problems. First, are the deaths of thousands of patients caused by taking calcium channel blockers when safer more effective alternatives could have been used. Second, there is little question that untreated hypertension and its attendant risks--heart attacks and strokes amongst others--extracts a massive toll of lost lives and impaired health amongst Americans and people all over the world. But the failure to put strong warnings on labels will inevitably lead to dangerous public cynicism about the treatment of hypertension. Public campaigns to diagnose and treat hypertension which keep patients in the dark about the fact that some drugs--such as calcium channel blockers--lower high blood pressure but actually increase the risk of death may well

lead patients to stay away from those drugs which not only lower high blood pressure but actually decrease the death rate from complications of hypertension.

In 1993, the last year for which we have data, the four top selling calcium channel blockers alone had more than $2 billion ($2.117 billion) in sales in the U.S., lead by Pfizer's Procardia XL (nifedipine) with $1.082 billion in sales. Advertising for anti-hypertensive drugs in the January 18, 1996 issue of the *New England Journal of Medicine* revealed the advertising bias leading to these astounding sales. Of the 15 pages of advertisements for antihypertensive drugs in that issue, none were for diuretics, or for beta-blockers, the two classes of drugs which are more effective and safe to use. Ten of the 15 pages were for calcium channel blockers (the other 5 were for ACE inhibitors) including, for Pfizer's Procardia XL (nifedipine) the statement, "Trust the Experience".

Doctors stopped a number of randomized controlled trials because of evidence of harm in people getting calcium channel blockers compared to other drugs. They had thus fulfilled their obligation to protect patients who have given informed consent to participate in these experiments. Why, via warning labels, are millions of patients currently using these drugs not being similarly warned?

Last fall, a nationwide market research study concerning calcium channel blockers was conducted which included 28 cardiologists and 15 general or family practice doctors. The major findings were:

* 21 of the 43 doctors indicated a drop in calcium channel blocker usage in which long acting calcium channel blockers had become second, third, or even forth line treatments prescribed only when diuretics, beta-blockers or ACE inhibitors are contraindicated or not sufficient by themselves.

* Many, especially those who lecture at continuing medical education meetings, predict the decline in calcium channel blocker use will continue or even accelerate as doctors have time to consider the implications of the research.

* One cardiologist said: "This has struck me to the core--and I was a confirmed calcium channel blocker user."

According to a drug industry analyst, the last part of 1995 saw, for the first time, a decline in prescriptions for calcium channel blockers. Thus, the research shows that as doctors become more aware of these serious dangers they are less likely to prescribe calcium channel blockers.

By law and the pertinent regulations (Federal Food Drug and Cosmetic Act 21, U.S.C. Section 355(e)(3),and 21 C.F.R. 10.30), the FDA is obligated to keep up to date and act on new information not available at the time of approval by promptly putting warnings on drugs when new evidence supports such warnings. The history of significant labeling changes is all too often a history of dangerous delays from the time the information strongly suggesting the need for a labelling change is available until the change is actually made. Warning labels on aspirin concerning Reye's Syndrome is a tragic but clear example. By October 1981, studies showed that children with flu or chicken pox who were given aspirin were significantly more likely to develop Reye's Syndrome than children not given aspirin. Because the aspirin industry and many of its hired hands felt obligated to find fault with these studies, warning labels were not required until early 1986. Because of the delay, thousands of children needlessly suffered death or brain damage from Reye's Syndrome, a disease which largely disappeared in this country when warning labels were required.

When the FDA fulfills its legal obligation and requires warnings in doctor and patient labeling concerning the dangers of calcium channel blockers, the use of these drugs will drop to between one-tenth and one-twentieth of what it is at present. As we stated in our petition patients should consult with their physicians before altering any of their medications.

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