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STATEMENT OF SIDNEY M. WOLFE, M.D. AND LARRY D. SASICH, PHARM.D., M.P.H. OF PUBLIC CITIZEN'S HEALTH RESEARCH GROUP BEFORE THE FDA'S CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE ON THE ANTIARRHYTHMIC DRUG DOFETILIDE (TIKOSYN)

January 28, 1999

National Institutes of Health, Natcher Conference Center

Public Citizen had requested (January 7th) through the Freedom of Information Act (FOIA) access to the Food and Drug Administration (FDA) and other data sent to your advisory committee concerning the safety and efficacy of dofetilide (Tikosyn), a type III antiarrhythmic drug, for which Pfizer Pharmaceuticals is seeking approval. Our request was denied and we are deeply concerned about the evidence that this drug can cause potentially life-threatening heart rhythm disturbances even though it may be approved to treat or prevent heart rhythm abnormalities.

Despite not being allowed access to these data and the fact that the peer reviewed medical literature is not an adequate substitute for the FDA reviews of safety and efficacy we do have serious concerns based on a review of the published literature about the safety of dofetilide because of its proarrhythmic effects and association with *torsade de points* (a potentially life-threatening heart rhythm disturbance). We are also apprehensive about the use of an antiarrhythmic drug to prevent the recurrence of an arrhythmia after the increased risk of death was found with the class IC antiarrhythmic drugs in the Cardiac Arrhythmia Suppression Trial (CAST)[1] in the early 1990s.

Several studies in patients with atrial fibrillation or flutter or normal volunteers, have led to our concern over the potential of this drug to cause arrhythmias. In a study of IV dofetilide in 16 patients with recent onset atrial fibrillation, two of 15 patients (13%) completing the study suffered episodes of *torsade de points.*[2] In a study of ten healthy

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[1] Echt DS, Liebson PR, Mitchell LB, and the CAST Investigators: Mortality and morbidity in patients receiving encainide, flecanide or placebo. The Cardiac Arrhythmia Suppression Trial. *New England Journal of Medicine* 1991; 324:781-788.

[2] Sedgwick ML, Lip G, Rae AP, et al. Chemical cardioversion of atrial fibrillation with intravenous dofetilide. *International Journal of Cardiology* 1995;49:159-166.

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male volunteers given oral dofetilide one subject exhibited asymptomatic polymorphic ventricular tachycardia when his QT_c interval was excessively prolonged.[3] The authors felt that this may have been due to a repolarization abnormality unmasked by the drug. In another study, *torsade de points* occurred in two (3.2%) of 62 patients with sustained atrial fibrillation or flutter who received at least one IV infusion of dofetilide.[4] These authors cautioned that "The efficacy of a drug for terminating an arrhythmia is not necessarily equivalent to its efficacy for preventing recurrence . . ." and we would add that it may not be as safe either. They also pointed out that "Dofetilide manifests electrophysiologic features that may predispose to aberrant ventricular conduction and aberrant conduction during atrial fibrillation that may be difficult to distinguish from short runs of ventricular tachycardia."

Public Citizen is on record as being deeply troubled about drugs that have been approved by the FDA with known safety problems that were subsequently withdrawn from the market after many deaths and injuries. The three most recent examples are dexfenfluramine (Redux), mibefradil (Posicor) which three members of this advisory committee thought should not have been approved, and bromfenac (Duract). We are concerned that this trend is continuing with the recent approval of cilostazol (Pletal) for the treatment of intermittent claudication, a painful but non-life-threatening condition that is most effectively managed by a structured program of exercise and the possible approval of dofetilide.

We urge that this committee decide that dofetilide, a drug that can cause potentially life-threatening arrhythmias, should not be approved to prevent recurrent arrhythmias, because, if approved, the tragic experience of the class IC antiarrhythmic drugs will be relived.

The treatment of atrial fibrillation with digitalis to control the rate and warfarin to prevent thromboembolic events is very likely safer than the long-term use of a drug such as dofetilide.

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[3] Tham TCK, MacLennan BA, Burke MT et al: Pharmacodynamics and pharmacokinetics of the class III antiarrhythmic agent dofetilide (UK-68,798) in humans. *Journal of Cardiovascular Pharmacology* 1993; 21:507-512.

[4] Falk RH, Pollak A, Singh SN et al (for the Intravenous Dofetilide Investigators): Intravenous dofetilide, a class III antiarrhythmic agent, for the termination of sustained atrial fibrillation or flutter. *Journal of the American College of Cardiology* 1997; 29:385-390.