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Joan Claybrook, President

August 10, 1995

CITIZENS' PETITION

David A. Kessler, M.D., J.D.
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

CITIZENS' PETITION TO REQUIRE A WARNING ON QUINIDINE

Dear Dr. Kessler:

Public Citizen, a nationwide consumer organization with about 90,000 members, and Frank Marcus, M.D., a Professor of Medicine and Cardiology from the University of Arizona School of Medicine, hereby petition the FDA, pursuant to the Federal Food, Drug and Cosmetic Act 21, U.S.C. Section 355(e)(3), and 21 C.F.R. 10.30, to immediately add warning labels on quinidine and strengthen the warning on other Class I antiarrhythmic drugs.

By allowing drug companies to fail entirely to warn physicians in the drug labeling of the clear evidence of increased risk of death with the top-selling antiarrhythmic drugs quinidine sulfate (Quinidex Extentabs,Wyeth-Ayerst), quinidine gluconate (Quinaglute Dura-Tabs, Berlex Labs) and quinidine polygalacturonate (Cardioquin, Purdue Frederick), and their generic equivalents, the FDA has been contributing to thousands of unnecessary and preventable drug-induced deaths each year. In 1992, there were over 2.6 million prescriptions filled for quinidine-containing drugs in U.S. retail pharmacies. Thus, hundreds of thousands of Americans use these drugs each year, the majority being at significantly increased risk of death from their use.

A summary of the evidence to support this includes:

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1. The Cardiac Arrhythmia Suppression Trial (CAST) proved that treatment of mild heart rhythm disturbances after heart attacks with two other Class I antiarrhythmic drugs (flecainide and encainide) was harmful, increasing risk of death or cardiac arrest by 2.5 times. Testing of a third drug in the class was halted for safety reasons. The FDA has said it is prudent to assume that these risks apply to all other antiarrhythmic drugs in Class I and promised Congress, in 1991, to relabel all of them accordingly.

2. A 1992 meta-analysis of 51 randomized clinical trials of Class I drugs, including quinidine, shows that their use to treat heart rhythm disturbances after heart attacks was harmful and increased the risk of death.

3. A 1990 meta-analysis of six randomized controlled trials of chronic atrial fibrillation showed quinidine increased the risk of death by 2.9 times, compared to a placebo.

4. A 1991 meta-analysis comparing quinidine to four similar Class I drugs for suppression of mild heart rhythm disturbances showed the risk of death was higher for quinidine than for the other drugs. All Class I antiarrhythmic drugs except quinidine now have warnings about increased risk of death.

5. In Congressional testimony four years ago in April, 1991, Dr. Robert Temple, the Director of FDA's Center for Drug Evaluation, said, after reviewing the 2.5 -fold increase in mortality in patients in the CAST (see 1., above), said "we are in the process of relabeling essentially all antiarrhythmic drugs to recommend their use only in immediately life-threatening illnesses to say that use in lesser arrhythmias is generally not recommended ...that the recommendations of CAST should probably be applied to all these other drugs...."

6. Almost two years ago, FDA's own Director of the Division of Cardio-Renal Drugs, Dr. Raymond Lipicky, under whose authority these drugs fall, said: "We are going to change the quinidine labeling. Quinidine, as far as a mortality effect, beat flecainide in causing more deaths in chronic PVC [premature ventricular contraction--an arrhythmia] trials." [Flecainide has had a warning concerning increased risk of death since 1990.]

ACTIONS REQUESTED

We hereby request the following immediate actions:

1. NEW WARNING FOR QUINIDINE

The following boxed warning to be in bold type should appear at the beginning of the manufacturer's product information for all Class I antiarrhythmic drugs. At present, all drugs in Class I except quinidine have some warning concerning increased risk of death but only flecainide has a boxed warning and it is not sufficiently strong.

The use of Class I antiarrhythmic drugs, such as quinidine, has increased the risk of death when used in patients with non-life-threatening cardiac arrhythmias.
Antiarrhythmic drugs have not been shown to improve survival in patients with ventricular arrhythmias.

2. Require that a stronger warning (as above) be boxed in bold type and placed at the beginning of the manufacturer's product labeling for procainamide (Procan), disopyramide (Norpace), tocainide (Tonocard), mexiletine (Mexitil), flecainide (Tambocor), propafenone (Rythmol), and moricizine (Ethmozine).

3. Quinidine-containing drugs are the only Class I antiarrhythmic drugs currently approved for ventricular arrhythmias that are not life-threatening, an indication that has been shown to be harmful in clinical trials. Quinidine-containing products should have the same indication as other Class I antiarrhythmic drugs which should read as follows:

Quinidine-containing drugs are indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that, in the judgement of the physician are life-threatening. Because of the pro-arrhythmic effects of quinidine-containing drugs, their use with lesser arrhythmias is not recommended. Treatment of patients with asymptomatic ventricular premature contractions should be avoided.

4. Immediately inform all U.S. physicians, pharmacists and other health professionals via the *FDA Medical Bulletin* about these new restrictions and warnings.

BACKGROUND

In 1989 and 1992, the Cardiac Arrhythmia Suppression Trial (CAST), clearly demonstrated that it was harmful to treat asymptomatic premature heartbeats in recent heart attack survivors. Not only was the expected benefit-prevention of sudden cardiac death--found not to exist, but the drugs increased the risk of sudden death by 2.5 times for two drugs, Enkaid (encainide), now no longer marketed in the U.S. and flecainide (Tambocor), still on the market but with a strong warning label as mentioned above. For a third antiarrhythmic drug, moricizine (Ethmozine), five times as many patients on the active drug died suddenly during the two-week titration period as those on placebo, causing cancellation of the trial on safety grounds[1,2] and on the basis that it was unlikely that a beneficial effect of the drugs would be observed if the trial were completed.

After publication of the CAST[1,2], the FDA moved to require a warning on all Class I antiarrhythmic drugs (see Table 1, page 6). The rationale was that increased death and non-fatal cardiac arrest--a risk clearly outweighing any known benefits--was found with the use of these drugs in patients with asymptomatic non-life-threatening ventricular

arrhythmias even if they had not had a previous heart attack. Despite Dr. Lipicky's above statement almost two years ago that quinidine was just as dangerous as flecainide---such labeling has not been required for quinidine even though Dr. Lipicky said the FDA would require such labels on quinidine.

The current labeling for quinidine, along with failing to warn of the increased risk of death that all the other Class I drug labels include, actually indicates the drug for "premature atrial and ventricular contractions" without any qualifications that use is not indicated for non-life-threatening arrhythmias, which constitute the largest fraction of use of the drug.

Following the results of CAST, there was a special meeting of the FDA Cardiovascular and Renal Drugs Advisory Committee on this topic. One of their recommendations was that "the administration of these agents [Class 1A, 1B, or IC antriarrhythmic drugs] to treat asymptomatic, non-life-threatening ventricular arrhythmias should not be a labeled indication of any of these agents."[3]

EVIDENCE FOR INCREASED RISK OF DEATH WITH QUINIDINE

A 1989 meta-analysis of studies on long-term Class I antiarrhythmic therapy after heart attack found that this class of drugs reduce premature ventricular contractions (PVCs), but "probably shorten survival."[4] Though this meta-analysis did not include any quinidine studies, the authors noted that these drugs work through similar mechanisms. A more recent (1993) meta-analysis of prophylactic antiarrhythmic agents found that the Class I drugs suppress arrhythmias but do not suppress sudden death. These authors concluded that **"the routine use of Class I antiarrhythmic agents after myocardial infarction is associated with increased mortality"** and **"the harm of these agents does not appear to be confined to any one agent or subclass of agents."**[5] [Emphasis added.]

A 1991 meta-analysis of four controlled clinical trials found that quinidine is more toxic than other members of the Class I antiarrhythmic class. The risk of death was calculated to be three times greater with quinidine treatment than with the four other Class I antiarrhythmics examined (Odds Ratio, 3.08; 95% CI, 0.99 to 9.60).[6] All four of these drugs--flecainide (Tambocor), mexiletine (Mexitil), tocainide (Tonocard) and propafenone (Rythmol)--are currently marketed in the U.S., and carry the FDA required warning concerning increased risk of death when used in patients with asymptomatic non-life-threatening ventricular arrhythmias.

More than 20 years ago, two randomized placebo controlled trials were published which tested the effect of prophylactic quinidine treatment on the risk of death after heart attack. [7,8] Both were small and of short duration but neither provided any evidence of a benefit to patients.

Coplen et al.[9] examined the safety and efficacy of quinidine in the maintenance of

sinus rhythm after cardioversion from chronic atrial fibrillation (AF). Their meta-analysis examined all randomized controlled trials of quinidine maintaining sinus rhythm after cardioversion published between 1966 and July 1989. The six trials they examined included 808 patients. The cardiac diagnosis reported for these six trials did not include previous heart attack. Twelve patients died while taking quinidine and three patients died in the control group. A lethal ventricular arrhythmia was reported as sudden cardiac death in three of seven quinidine treated patients in which the cause of death was specified by the authors. Ventricular arrhythmia may have been the cause of death in some or all of the five other patients in which the mechanism of death was unclear. The OR (increased risk) of dying in the quinidine group was 2.98; 95% CI, 1.1 to 8.3; $p < 0.05$.

These authors concluded that quinidine treatment was more effective than no drug in suppressing recurrences of atrial fibrillation but appears to be associated with increased total mortality.

INCONSISTENT LABEL WARNING FOR CLASS I ANTIARRHYTHMIC DRUGS

The FDA has not consistently applied its own requirement for an increased risk of death warning to Class I antiarrhythmic drugs. Quinidine containing drugs have no warning; only the warning for flecainide (Tambocor) is boxed; the warning is not in bold type for two drugs, procainamide (Procan) and propafenone (Rythmol); and, for the drugs with a warning, none are at the beginning of the manufacturer's product information.

Table 1 on the following page summarizes the inconsistent warning of increased death with Class I antiarrhythmic drugs as found in the 1995 edition of the *Physician's Desk Reference*.

Table 1 - Current Increased Mortality Labeling
for the Oral Class I Antiarrhythmic Agents Marketed in the United States.

Drug	Antiarrhyth-mic Class	Label Warning	Warning Boxed	Warning in Bold Type	Warning Appears at Beginning of Product Labeling
Quinidine	**IA**	**NO**	**NO**	**NO**	**NO**
Procainamide	IA	Yes	No	No	No
Disopyramide	IA	Yes	No	Yes	No
Tocainide	IB	Yes	No	Yes	No
Mexiletine	IB	Yes	No	Yes	No
Flecainide	IC	Yes	Yes	Yes	No
Propafenone	IC	Yes	No	No	No
Moricizine	I[1]	Yes	No	Yes	No

[1] Class I agent, but does not fit into a subgroup.

INAPPROPRIATE USE OF CLASS I ANTIARRHYTHMICS CONTINUES

Table 2 below summarizes the results of a National Heart Lung and Blood Institute survey of how 730 U.S. physicians would treat patients with asymptomatic ventricular arrhythmias such as non-sustained ventricular tachycardia (NSVT) or asymptomatic ventricular premature depolarizations (VPD). This survey, conducted in 1992 after the results of the CAST were known, showed widespread use by cardiologists and generalists for patients with non-life-threatening arrhythmias with these drugs, thus actually increasing the risk of death.[10] In addition to the data in the table below, the study found that, whereas very few physicians (under 3%) were prescribing Class IC drugs (see Table 1, page 6) such as flecainide for NSVT, 50% of physicians were prescribing Class IA antiarrhythmics, of which quinidine has 60% of the market. Thus, physicians were approximately 10 times more likely to prescribe quinidine for this arrhythmia than to prescribe flecainide and the other Class IC drugs combined, almost certainly reflecting the absence of a warning label for quinidine.

Sincerely,

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Table 2 - Summary of Survey Results of How 730 U.S. Physicians Would Treat Patients with Asymptomatic Ventricular Arrhythmias

Physician Specialty	Would Treat Asymptomatic NSVT[1] with Class I AAD[2]	Would Treat Asymptomatic VPD[3] with Class I AAD	Would Treat NSVT with Class I AAD	Would Treat VPD After MI with Drug or Device
Generalists	28.3%	46.4%	49%	44.2%
Cardiologists	23.5%	47.2%	51.7%	22.1%

[1] Nonsustained ventricular tachycardia, [2] Antiarrhythmic drug, [3] Ventricular premature depolarizations

CONCLUSION

Quinidine has toxicity at least as great and perhaps greater than the other Class I antiarrhythmic drugs. It is illogical and dangerous that a warning has not been required on quinidine-containing drugs when it is required on the other Class I antiarrhythmic drugs. Likewise, it is incomprehensible that quinidine is indicated for a use explicitly not recommended for the other Class I antiarrhythmic drugs--ventricular arrhythmias that are not life-threatening. The inappropriate prescribing of Class I antiarrhythmic drugs continues to be widespread. The warnings on these drugs--especially quinidine--must be strengthened and made more prominent to prevent heart patients from dying needlessly.

By failing to warn physicians of the dangers of quinidine-containing drugs--as FDA promised to do four years ago and again over two years ago--the FDA is contributing to thousands of preventable deaths each year. We urge you to act as quickly as possible on the enclosed petition in order to spare many heart patients from the life-threatening risks of quinidine and quinidine salts. In addition, the strengthened warnings on other Class I antiarrhythmic drugs are essential to protect the public's health.

CERTIFICATION

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

REFERENCES

1. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989;321:406-12.

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4. Hine LK, Laird NM, Hewitt P, Chalmers TC. Meta-analysis of empirical long-term antiarrhythmic therapy after myocardial infarction. JAMA 1989;262:3037-40.

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8. Jones DT, Kostuk WJ, Gunton RW. Prophylactic quinidine for the prevention of arrhythmias after acute myocardial infarction. Am J Cardiol 1974;33:655-60.

9. Coplen SE, Antman EM, Berlin JA, Hewitt P, Chalmers TC. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. Circulation 1990;82:1106-16.

10. Rosenberg Y, Schron E, Stylianou M, Parker A. Treatment of ventricular arrhythmias after the cardiac arrhythmia suppression trial (CAST): a survey of US physicians. J Am Coll Cardiol 1995;389A[abstract].