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Joan Claybrook, President

September 8, 1994

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

Dear Dr. Kessler:

Public Citizen's Health Research Group hereby petitions the FDA to immediately ban the widely-used prescription drug quinine sulfate--2.16 million prescriptions filled in 1992--for treatment or prevention of nocturnal leg cramps.¹ The medical reasons for the ban of the prescription products--lack of evidence of efficacy and serious dangers--are the same as those just reviewed in the recently issued (August 22, 1994) FDA regulation concerning the ban of all over-the-counter (OTC) forms of quinine sulfate for leg cramps. Thus, no such OTC drugs may be introduced into interstate commerce after February 22, 1995. The authority to ban prescription quinine sulfate for leg cramps is the Food, Drug and Cosmetic Act 21 U.S.C. Section 355 (e)(3), and 21 C.F.R. 10.30.

In the August 22nd *Federal Register* notice concerning the OTC ban, the FDA cited a review of adverse drug reaction reports it received from 1969 through June 1992. The FDA found 107 adverse reaction reports in which quinine appeared to have been used for treatment of leg cramps. Of these:

There were 60 serious adverse reactions involving 16 deaths, 4 cases of disablement and 40 hospitalizations not involving death or disablement (*Federal Register*, August 22, 1994, page 43236).

(It should be noted that the FDA's reports of deaths and serious injuries from quinine sulfate contain substantial numbers of cases in which the prescription versions or the OTC versions of the drug were implicated.)

¹ Although the major prescription product (Quinamm) and the major OTC products (Legatrin and Q-Vel) are sold exclusively for leg cramps, a small amount of other prescription quinine sulfate products are prescribed for treatment of malaria. This petition does not intend to interfere with this use.

On page 43240, the *Federal Register* notice went on to cite:

Reports in the literature have identified quinine sulfate [in doses typically recommended for the prevention and/or treatment of nocturnal leg cramps] to be the causative agent in photosensitivity dermatitis, psychosis, disseminated intravascular coagulation [blood clotting] and hemolytic uremic syndrome.

Spontaneous adverse reaction reports filed with the FDA show:

reasonably unconfounded reports of thrombocytopenia [low platelet counts], hemolytic anemia [destruction of red blood cells], leukopenia [low white blood cell counts], granulocytopenia [low counts of one type of white blood cell], anaphylaxis [an acute reaction in which spasm of the larynx can cause choking or death], hypersensitivity syndrome, severe skin reactions, liver abnormalities, renal failure and death.

On page 43242 the *Federal Register* notice states:

The agency does not consider it likely that a warning statement in quinine product labeling would be of significant value because it is impossible to prospectively identify the groups at risk.

And on page 43251, the *Federal Register* notice states:

Given the benign nature of nocturnal leg muscle cramps, the failure of the clinical studies to demonstrate efficacy of quinine sulfate in this condition, the evidence of the symptoms of quinine toxicity at the OTC doses employed for leg cramps in a proportion of the target population, and the potential for serious, life-threatening and fatal hypersensitivity reactions to quinine, the agency concludes that quinine is not safe for OTC use in the treatment and/or prevention of nocturnal leg muscle cramps.

In addition to requesting that the prescription versions of quinine sulfate for leg cramps be banned, the FDA deserves serious criticism for failing to warn the American public of the imminent ban of widely-sold OTC quinine sulfate products intended solely for the treatment and prevention of nocturnal leg cramps such as Q-Vel (Ciba Consumer) and Legatrin (Columbia). **We urge all patients who have these products to return them to the pharmacies or other stores where they were purchased for a refund. We also urge that the OTC quinine products immediately be taken off the shelves of stores where they are being sold.**

**Current Marketing and Use of Quinine:
2.16 Million Prescriptions, \$28 Million in Sales in 1992**

The most recent data on prescriptions filled in retail pharmacies for quinine sulfate products, including the brand name product, Quinamm and many different generic versions, was 2.4 million prescriptions filled in 1992.² According to drug industry monitoring data, approximately 90% of these prescriptions were for the prevention and treatment of leg pain. Thus, in 1992, there were 90% of 2.4 million or 2.16 million prescriptions filled for people using quinine sulfate for leg pain. As mentioned before, the top-selling product, Quinamm (Marion Merrell Dow), is promoted and prescribed exclusively for leg pain. At an average retail cost of \$13 for a 30 day supply of the drug (including Quinamm and the generic versions), the annual retail sales for quinine sulfate prescriptions for leg pain were approximately \$28 million dollars (2.16 million times \$13).

Estimated Number of Cases of Serious Adverse Reactions

One of the very well-documented serious adverse reactions caused by quinine sulfate is thrombocytopenia (low platelet counts) which involves the drug causing the patient to develop antibodies to their own platelets which is accompanied by a low level of platelets, the cellular components necessary for blood clotting to occur. In some cases, when this is quite severe, the patient can bleed to death.

Page 43242 of the August 22 *Federal Register* notice states that:

These three [reference study] sources provide a reasonably small range for the incidence of quinine induced immunologic thrombocytopenia (QIITP) that can be expected about 1:1000 to 1:3000.

Thus, with 2.16 million prescriptions a year filled for quinine sulfate for the treatment of leg cramps, if each person using the drug gets, for example, four prescriptions filled a year on the average, then over 540,000 people a year use the drug. With FDA's estimates of between one case of thrombocytopenia per 1000 patients and one per 3000 patients, this means an estimated 180 to 540 cases a year of this serious adverse reaction which can be fatal. This does not include the much larger number of other adverse reactions mentioned above.

OTC and Prescription Quinine for Leg Cramps: Same Dose Range

The dose of quinine sulfate in the about-to be-banned over-the-counter versions are in the same range as the doses in the prescription pills. For example, the top-

² National Prescription Audit, 1992. IMS, Plymouth Meeting, PA.

selling OTC brand, Legatrin (Columbia), contains 162.5 milligrams per pill and the recommended dose is two pills for treatment or prevention of leg cramps. Quinamm, the top-selling prescription version of this drug, is 260 milligrams per pill and the recommendation is to use one or two nightly. The generic versions of Quinamm are also 260 milligrams and the generic versions of Legatrin are either 200 milligrams or 325 milligrams.

Chronology of Delayed FDA Action on Quinine

1977 FDA Over-the-Counter Advisory Panel on Internal Analgesics and Antirheumatic Products concludes: "Until controlled studies show that a dose of not more than 325 milligrams daily [of quinine] is safe and useful for relief of nocturnal leg cramps the drug should not be available for OTC use for treatment of nocturnal leg cramps"

1985 FDA agrees with this lack of evidence of effectiveness and publishes a tentative final monograph, allowing the products to stay on the market in the interim until a final monograph is published.

December 1, 1988 Public Citizen's Health Research Group petitions to ban OTC use of quinine for leg cramps, and to require drug companies to immediately submit data on safety and effectiveness for prescription use. At the time of the petition, the FDA had received 8 reports of deaths from the use of these products.

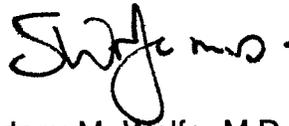
1994 FDA publishes a *Federal Register* notice with the long-overdue final rule concerning these drugs. The rule states that no over-the-counter products for the treatment or prevention of nocturnal leg muscle cramps may be introduced into interstate commerce after February 22, 1995, because they are not generally recognized as safe and effective. The reason for the relatively short time between publication of the *Federal Register* notice and the ban is, according to the FDA, because of the safety problems with the drug. The notice on page 43252 states:

In the doses used to treat or prevent this condition [nocturnal leg cramps], quinine sulfate has caused adverse events such as transient visual or auditory disturbances, dizziness, fever, nausea, vomiting or diarrhea. Quinine sulfate may cause unpredictable serious and life-threatening hypersensitivity reactions requiring medical intervention and hospitalization; fatalities have been reported. The risk associated with use of quinine sulfate, in the absence of evidence of its effectiveness, outweighs any potential benefit in treating and/or preventing this benign, self-limiting condition. Based on the adverse benefit-to-risk ratio, any drug product containing quinine or quinine sulfate cannot be considered generally recognized as safe.

Conclusion

Since the FDA has (quietly) announced the imminent ban of OTC quinine sulfate for leg cramps, since the basis of this is the lack of evidence of its effectiveness and substantial evidence of its danger, since the OTC and prescription versions of quinine sulfate are in the same dose range and since, in the six years since our 1988 petition the manufacturers of the prescription version of quinine sulfate have failed to submit, as requested in our petition, evidence of its safety and effectiveness, the FDA should immediately ban these prescription products for leg cramps. Failure to do so may result in legal action by our organization to force the FDA to uphold its legal responsibilities. I hope for a rapid response to this petition.

Sincerely,

A handwritten signature in black ink, appearing to read "Sidney M. Wolfe, M.D.", with a stylized flourish at the end.

Sidney M. Wolfe, M.D.
Director, Public Citizen's
Health Research Group