



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

October 23, 2002

Elizabeth Barbehenn, Ph.D.
Peter Lurie, MD
Sidney Wolfe, MD
Public Citizen
1600 20th Street NW
Washington, DC 20009-1001

Dear Doctors Barbehenn, Lurie and Wolfe:

I am writing in response to your letter of October 15, 2002, in which you comment on a letter written to the FDA by Dr. Gary Feinstein.

As stated in Title 21 CFR 10.30 (d), Citizen Petition, an interested person may submit written comments to the Dockets Management Branch on a filed petition, which comments become part of the docket file. We do not exclude/nor have the right to exclude any individual from expressing opinions. The commissioner or his designee make decisions on a scientific basis and take all comments into consideration when making a final determination.

Thank you for providing your additional comments. I will have them forwarded to the Dockets Management Branch for inclusion to the docket. Your comments will be taken into consideration as we make a determination to your initial petition.

Sincerely,

Janet Woodcock, MD
Director
Center for Drug Evaluation and Research

02P-0139

C2 / ANS



Buyers Up • Congress Watch • Critical Mass • Global Trade Watch • Health Research Group • Litigation Group
Joan Claybrook, President

October 15, 2002

Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Woodcock:

Dr. Gary Firestein, chairman of the Arthritis Advisory Committee, has written an "unsolicited" letter to the FDA concerning Public Citizen's petition to remove Arava (leflunomide) from the market due to its severe adverse effects including 130 severe hepatic reactions leading to at least 12 deaths.¹ He states that his conclusions are "based on the information provided in the petition".

This latter statement is difficult to understand since Dr. Firestein appears to have missed not only much of what we said in our petition but what is in the current FDA-approved label for leflunomide, as well. For example, he suggests that, "Based on the data provided by the petition, it would be appropriate to recommend a study of the relative toxicities of methotrexate and leflunomide in a more controlled setting." In fact, those studies have already been done. The label (and our petition) provide data from two one-year, randomized, controlled trials of methotrexate vs. leflunomide, the very data upon which leflunomide's approval was based.

The larger of these trials compared leflunomide directly with methotrexate (501 patients on leflunomide and 498 on methotrexate) and the smaller compared leflunomide with methotrexate and placebo (182, 182 and 118 patients/group, respectively). In the clinical trial with the most reliable data on liver function enzymes, a greater proportion of leflunomide-treated patients had high liver enzyme levels than those on methotrexate (2.5% of placebo, 2.7% of methotrexate, and 4.4% of leflunomide patients had ALT elevations greater than

¹ <http://www.citizen.org/documents/1614.pdf>

Ralph Nader, Founder

1600 20th Street NW • Washington, DC 20009-1001 • (202) 588-1000

Dr. Firestein relies again on "clinical experience" (rather than actual data) when he asserts that sulfasalazine is not as effective as leflunomide. He faults the clinical trial data showing that sulfasalazine is comparable to leflunomide⁶ as "likely due to inadequate dosing of comparators", yet, the comparator, leflunomide, was tested at the dose the FDA recommends (the same dose of leflunomide used in all pivotal clinical trials).

Without data from controlled trials (as opposed to the anecdotal data of Dr. Firestein) to determine the effects of rheumatoid arthritis drugs, physicians should be particularly wary of making statements about a drug's "effectiveness". (One must also differentiate effectiveness in terms of short-term benefits vs. actually extending life.)

Furthermore, the American College of Rheumatology 2002 Guidelines for RA⁷ discuss the difficulty of a correct RA diagnosis in the early stages of the disease and its tendency to wax and wane. Thus, for Dr. Firestein to imply that RA is a "medical emergency", requiring early intervention, no matter how little clinical trial data exists on a drug's long-term effects, has the potential to bankrupt patients (etanercept is \$15,000/yr and infliximab is \$14,000 - 37,000/yr)⁸ as well as potentially put them at risk of even more dangerous outcomes.

It is discouraging that we have a so-called expert in the field of rheumatology who, apparently, has not thoroughly read either our petition or the original label for leflunomide, yet feels free to attack our petition. We tried in our petition to present as much information as was available, to analyze it rigorously, and to provide references so that our statements could be checked; unfortunately, Dr. Firestein failed to do this.

A previous Chair of the FDA Arthritis Drugs Advisory Committee, Dr. David Yocum, wrote a letter supporting our petition for removal of leflunomide from the market. Dr. Yocum was as concerned as we were about leflunomide's "serious adverse events, the apparent inability to predict patients who might suffer from the severe and potentially life threatening complications and the apparent ineffectiveness of a wash out procedure".⁹

It would seem to us that the chairman of an FDA advisory committee has a duty to be rigorous and impartial in analyzing information and not a cheerleader for particular drugs, even if "unsolicited". We question his ability to provide the impartial and critical leadership needed for the Arthritis Advisory Committee.

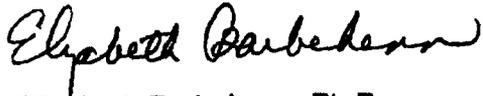
⁶ John Hyde, M.D., FDA Medical Officer's Review of leflunomide, September 3, 1998.

⁷ Guidelines for the management of rheumatoid arthritis, 2002 update. Arthritis and Rheumatism 2002;46:328-46. <http://www.rheumatology.org/research/guidelines/raquidelines02.pdf>

⁸ Ibid.

⁹ <http://www.citizen.org/pressroom/release.cfm?ID=1067>

Sincerely,



Elizabeth Barbehenn, Ph.D.
Research Analyst



Peter Lurie, M.D.
Deputy Director



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

cc: Dockets Management
Director, Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug
Products
Steven Galson, M.D.
Victor Raczowski, M.D.