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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

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

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3x the upper limit of normal). Although efficacies of methotrexate and leflunomide were equivalent in the smaller study, *methotrexate was clearly superior in the larger one* ($p < 0.0001$), providing the basis for our contention of both improved safety and greater efficacy for methotrexate.

Despite Dr. Firestein's belief in the ready educability of physicians, we found 34 MedWatch reports of "complications of maternal exposure", despite a black box warning of the contraindication of taking leflunomide during pregnancy. These 34 cases are surely an underestimate as MedWatch reports are estimated to represent only 10% of actual ADRs, at best. We are not the only ones to notice this problem. As noted in our petition, FDA's Risk Assessment Group has found that physician notification letters and drug label changes have had limited impact on drug prescribing.^{2,3}

The failure to warn pregnant women is made still worse by the drug's long half-life: 1 to 6 weeks in pharmacokinetic studies and almost 14 weeks in a population study. This means that it could take up to 18 months to clear the body of drug if no treatment to help clear the body is provided. Cholestyramine undoubtedly helps this clearing process, but how much is needed, for how long, and with what effectiveness are all unknowns. All the cholestyramine washout studies submitted by Aventis used single doses of leflunomide rather than dosing for the 10-12 weeks of drug therapy needed to reach (the higher) steady state blood levels. Thus, Dr. Firestein's statements about the evidence for "adequacy of cholestyramine" from "clinical practice" are anecdotal and simply not supported by any data: anecdotal data cannot replace the need for a well-designed trial.

One must be extremely careful about using "clinical practice" as a guideline for treatment. There are now a number of cases where what was once accepted as good "clinical practice" have been shown, instead, to be harmful. For example, although many observational studies had supposedly demonstrated benefits for hormone replacement therapy (HRT), a recent HRT trial was stopped early when it was demonstrated that the risks outweighed the benefits.⁴ Another recent study on the surgical treatment of osteoarthritis of the knee showed that the placebo group did as well as those who actually had the surgery.⁵ Therefore, it is not acceptable to only reference "clinical practice" as a source of information, as Dr. Firestein did.

² Graham, DJ, Drinkard CR, Shatin D, et al. Liver enzyme monitoring in patients treated with troglitazone. *Journal of the American Medical Association* 2001;286:831-833.

³ Smalley W, Shatin D, Wysowski DK, et al. Contraindicated use of cisapride: impact of Food and Drug Administration regulatory action. *Journal of the American Medical Association* 2000;284:3036-3039.

⁴ Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *Journal of the American Medical Association* 2002;288:321-333.

⁵ Moseley JB, O'Malley K, Petersen NJ, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *New England Journal of Medicine* 2002;347:81-88.

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,



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