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Food and Drug Administration
Washington, D.C.
To whom it may concern,

A recent Citizen's Petition was submitted to the Department of Health and Human Services regarding the safety of leflunomide. The authors requested that this drug be withdrawn from the market due to its toxicity. In light of the importance of these issues and the need place the petition's comments into perspective, I would like to offer my unsolicited opinion on the matter. As the chairman of the FDA Arthritis Advisory Committee, a practicing physician/rheumatologist for over 20 years, a translational researcher on the pathogenesis of rheumatoid arthritis (RA), and the executive director of a clinical trial center (cit.ucsd.edu), I believe that I can provide some insights that will be useful to the FDA. I should note that the specific details of individual patient histories are not available to me, and that my conclusions are based on the information provided in the petition and my own familiarity with the field.

The first issue that needs to be considered when evaluating the safety of any treatment for RA is that toxicity must be compared with the morbidity and mortality associated with active inflammatory synovitis. RA is not a benign condition, and many studies have demonstrated significantly higher mortality compared with controls (reviewed in Br J Rheumatol 1993;32 Suppl 1:28-37). This is especially true for patients with significant limitations on their activities of daily living, evidence of active inflammatory disease (e.g., high CRP), or involvement of many joints. While the impact of treatment on mortality is not fully understood, recent information suggests that effective treatment can prolong life (Lancet 2002; 359:1173-7). The mechanism of improved survival is not established, but is probably directly related to suppression of synovial and systemic inflammation. The impact of active RA on quality of life also needs to be considered when evaluating the risk/benefit ratio of a therapeutic agent. In other words, merely describing the potential toxicity of an agent in a vacuum is not only insufficient but can be misleading.

-- Because of the serious long-term consequences of active RA, rheumatologists have become increasing aggressive in its management. Immunosuppressive agents, cytokine antagonists, anti-metabolites, and combination therapy have become mainstays. Instead of relying on the now outdated "pyramid" approach, treatment is initiated early and is accelerated rapidly in order to suppress inflammation (Am J Med. 2001;111:498-500). Clinical trials using aggressive management, such as the **COBRA** trial and
. . many others, have demonstrated improved outcomes compared with conservative approaches. In this context,,the conservative and risk-averse recommendations of the Citizen's Petition clearly fail to take into account two key elements of,modern management: 1) poorly controlled RA is a dangerous and mnrhiri-jrnnriitinn- anrl 71•annrccc~ic trcatmcnt.rH~,altcr.the natural hietnni of tha riieaaec

address either the risk/benefit ratio or how the drug fits into the constellation of agents available for use in RA. For instance, there are a variety of assertions regarding the relative safety of methotrexate compared with leflunomide. Perhaps most important is the putatively lower rate of hepatotoxicity of the former. The comparative data are not derived from controlled databases, but from voluntary physician reporting. There is a well-described bias introduced when comparing toxicity of established agents to new agents that is clearly evident in this analysis. There is also little information on the use of concomitant drugs or the assiduousness of monitoring that could have prevented serious adverse events. Therefore, it is impossible to draw a conclusion regarding the relative rates of serious adverse events based on this information. The comments related to the long half-life of leflunomide raise reasonable concerns; however, clinical practice has supported the adequacy of cholestyramine in many cases where toxicity has been observed. 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. However, withdrawing an effective agent like leflunomide based on this limited information is both unjustified and counterproductive.

Perhaps the most important consideration in this discussion is how leflunomide should be used compared with other anti-rheumatic agents. Even if one assumes that methotrexate is a safer agent, current clinical practice guidelines indicate that leflunomide should be primarily administered to patients that have an inadequate response to methotrexate or have other contraindications. This makes comparisons of the relative toxicities moot, since patients that receive leflunomide would, by definition, have active disease and already received a putatively safer agent. Since we already know that active RA is an unacceptable alternative, then we are obliged to advance therapy using agents that are either less effective, more toxic, or have other undesirable attributes (e.g., expense or requirement for parenteral administration).

The alternatives to leflunomide suggested in the petition under these circumstances do not accurately represent state-of-the-art clinical practice. For instance, the use of "Rest and nutrition" as recommended by the Merk Manual is part of the outdated pyramid approach that does not recognize the long-term consequences of active RA. Of the "slow acting" agents recommended, two (gold and penicillamine) have not been used by most rheumatologist for over a decade due lack of efficacy and toxicity that far exceeds leflunomide. Hydroxychloroquine and especially sulfasalazine are stated to be equivalent to methotrexate and leflunomide. Sulfasalazine has been used extensively to treat patients with RA, especially in Europe. However, clinical experience in the United States does not support the assertion that it is as effective as methotrexate or leflunomide. The reported equivalence with sulfasalazine is likely due to inadequate dosing of comparators or type II errors due to underpowered studies. Immunosuppressive agents, including cyclosporine and azathioprine, have considerable toxicity and limited efficacy. Reliance on a tertiary source like the Cochrane Library or the Merck Manual as in the petition to determine the relative efficacy does not necessarily provide the most up to date or useful information.

Overall, patients that have an inadequate response to methotrexate are typically treated with a TNF inhibitor, leflunomide, or sulfasalazine (either alone or, more commonly, in combination). The selection of a particular agent depends on the patient's particular circumstances. Moreover, the percentage that respond to each of these drugs is limited, which means that several might be tried to determine the optimum combination. For instance, only 15% of patients failing methotrexate that receive the TNF inhibitors have an ACR70 response and only about 30% achieve an ACR50 response. The response rates for sulfasalazine are likely lower. Therefore, most patients will require considerable experimentation to find the best combination of drugs. Removing one of these key agents from our armamentarium would be a major setback to their management and is unjustified.

The final comments in the petition relate to the ineffectiveness of changing labels or educating physicians. On the contrary, the dissemination of information through the physician and patient

community is now rapid and has high penetration. For instance, new guidelines to assess patients receiving TNF inhibitors for prior tuberculosis exposure had a major impact on clinician practice. The rapidity of processing new information is especially true for RA because new anti-rheumatic drugs are mainly prescribed by subspecialists. The notion that rheumatologists do not modify their practice after appropriate education is simply untrue and is likely based on outdated information. The influence of patient advocacy also should not be underestimated. In my own clinical practice, the majority of patients receiving leflunomide specifically asked about the safety issue.

In conclusion, vigilance in post-marketing safety is a major concern and one must be ready to act if appropriate signals are observed. In the case of leflunomide, one must be cognizant of the risks of uncontrolled RA, the relative lack of efficacy for the alternatives to methotrexate, and the contribution of inadequate monitoring or inappropriate combination therapy to severe reactions. Leflunomide is an effective agent in RA that decreases inflammation, improves quality of life, and slows the progression of disease. The information provided by the petition does raise questions that should be addressed with appropriate studies, and the concomitant use with methotrexate should be carefully addressed. However, withdrawing the agent is simply not justified with the current information and would lead to increased morbidity (and possibly mortality) in RA patients that do not respond to methotrexate.

Sincerely,

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Chairman
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