



FDA Meeting March 2003: Update on the Safety of New Drugs for Rheumatoid Arthritis Part III: Safety and Efficacy Update on Leflunomide (Arava®)

The FDA Arthritis Advisory Committee met on March 5, 2003, to discuss updated issues related to the safety and efficacy of leflunomide (LEF). Information from the FDA meeting is available at <http://www.fda.gov/ohrms/dockets/ac/acmenu.htm>. Safety issues concerning LEF, particularly related to potential hepatotoxicity, have been the subject of two previous ACR Hotlines (August 2001, April 2002; available at www.rheumatology.org). In March 2002, a citizen's petition was submitted to the FDA by the group Public Citizen requesting that the agency remove LEF from the market based primarily in response to Medwatch reports of acute liver failure (reviewed in the [April 2002 ACR President's Column](#)). The March 2003 FDA meeting followed a yearlong assessment by the Agency of the most recent safety data concerning LEF. In addition, the committee considered data potentially supporting an additional indication for LEF, for improving physical functioning of patients with rheumatoid arthritis.

The yearlong, comprehensive review of safety data for LEF included analysis of the following databases:

- A database of 2,900 subjects on LEF in controlled clinical trials with a median exposure of over six months.
- Three independent medical claims databases comprising over 5,400 subjects treated with LEF for a mean of over 12 months.
- Data from the National Databank of Rheumatic Diseases on over 5,000 subjects treated with LEF for a mean of over 12 months.
- A database of hospitalizations for acute liver failure from a consortium of 17 liver transplant centers.
- The Adverse Event Reporting System (AERS) that represents the database of all Medwatch reports received by the FDA.

The FDA Division of Arthritis, Analgesic and Ophthalmic Drug Products reached the following conclusions regarding LEF and liver injury:

- LEF is associated with a three-fold elevation of liver enzymes in 2-4% of subjects compared to 1-2% in the placebo-treated groups as is currently identified in the drug label
- Hospitalization for apparent drug-related hepatitis was identified in the databases at a rate of approximately 0.02% or 1/5000 patients
- There were no cases of hepatocellular necrosis with jaundice (an event with a mortality association of greater than 10%) in the databases of 13,700 subjects

There are few cases of LEF-induced serious liver injury or acute liver failure in postmarketing surveillance. Through the Medwatch system, the FDA has received several reports of possible LEF-induced acute hepatic failure. The majority of these reports were highly confounded by the concomitant use of agents known to be potential hepatotoxins, co-morbidity affecting the liver or otherwise inadequate case information so that no conclusions about the relationship between these reports of serious liver injury or acute liver failure and the use of LEF could be drawn.

The FDA presentation concluded that the incidence of elevated liver function tests is in the range of 2-4% but serious hepatotoxicity, such as hepatocellular jaundice and acute liver failure, is rare based on:

- The small number of post-marketing reports of acute liver failure
- The absence of acute liver failure as well as a less severe degree of acute liver injury, (hepatocellular necrosis with jaundice) in a database of over 13,000 subjects
- Data suggesting that hospitalization for drug-induced liver injury may occur with a frequency of well under 0.02%
- Review of the FDA Medwatch database showing that the reporting rate for acute liver failure and fatal hepatotoxicity associated with LEF is well below that for previously identified drugs with serious hepatotoxicity such as INH, valproate, trovafloxacin bromfenac and troglitazone

The committee unanimously voted to recommend that LEF remain on the market and commented that it continued to represent a valuable therapeutic in the armamentarium for the treatment of rheumatoid arthritis.

In addition, the committee received data supporting the efficacy of LEF for the improvement of physical function. Such data, based on assessments using the Health Assessment Questionnaire, reflect symptomatic improvement. The committee voted to recommend that labeling be updated to include information on the demonstrated improvement in physical function.

The FDA will review these nonbinding recommendations forwarded by the Arthritis Advisory Committee.

The Bottom Line:

- While elevations in liver function tests are seen in 2-4% of LEF treated patients, serious hepatotoxicity is extremely rare.
- The Arthritis Advisory Committee of the FDA recommends that LEF remain on the market.
- LEF should receive additional labeling for improvement in physical function in patients with RA.

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