

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN
SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND
RESEARCH

DATE: December 20, 2002

TO: NDA 20-905

FROM: Paul J. Seligman, MD, MPH, Director, Office of
Pharmacoepidemiology and Statistical Science
(HFD-030)

SUBJECT: **NDA 20-905; Arava (leflunomide) Tablets**
(Superoffice Response to November 7, 2002
memorandum)

This memorandum documents my non-concurrence with the recommendation in the November 7, 2002 memorandum on severe hepatotoxicity and liver failure related to the administration of Arava (leflunomide) Tablets.

Background:

Fifty-four cases of serious hepatic injury temporally associated with the use of Arava (leflunomide) Tablets have been reported to FDA's Adverse Event Reporting System (AERS). Analysis of these cases indicates that the risk of hepatotoxicity associated with leflunomide extends beyond elevations in serum enzymes, as reported in the leflunomide labeling, to include severe hepatotoxicity and acute liver failure. The number and severity of reported cases of hepatotoxicity associated with leflunomide use constitutes an important safety signal that requires prompt attention.

In considering the appropriate regulatory and public health actions to take in response to this signal, it is essential that the risks associated with leflunomide, as documented in the November 7, 2002 memo, be weighed against its benefits. These include the drug's effectiveness for its approved indication (treatment of active Rheumatoid Arthritis in adults), disease severity in patients considered for treatment with the drug, and the availability of therapeutic alternatives. In addition, all options available to manage the range of risks associated with leflunomide administration must be carefully considered.

Rheumatoid arthritis is a severe debilitating disease for which there is no cure. For some of these patients, it is not unreasonable that considerable risks associated with a drug such as leflunomide may be acceptable if there is sufficient benefit associated with the therapy. These situations or the absence of such situations must be understood in weighing appropriate regulatory action.

The November 7, 2002 memo compares the risk profile of leflunomide to methotrexate. Before concluding that leflunomide has no place in the spectrum of treatments for rheumatoid arthritis, the full range of treatment modalities available to clinicians treating this condition must be assessed. The suggestion that methotrexate be used preferentially to leflunomide because of its better risk profile does not address situations where methotrexate is ineffective or inappropriate. The clinical benefits and risks of all drugs known to modify the disease process must be considered carefully before rejecting leflunomide as having no place in the spectrum of drug therapies available for rheumatoid arthritis.

The November 7, 2002 memo concludes that lack of proven risk management strategies leaves no alternative than to withdraw leflunomide from the market. There is evidence for some drugs in some situations that usual risk management strategies, such as labeling changes, boxed warnings, and letters to health care providers, do not substantially reduce contraindicated coprescribing or sustain increases in monitoring for side effects. However, it is difficult to conclude that these and similar measures are either uniformly or even usually ineffective based on these studies. Alternatively, other risk management tools appear to have been effective. For example, the November 7 review cites examples where restricting the distribution of a drug appears to be effective in ensuring that only the appropriate patients receive the drug and that the harmful side effects are minimized. Further, the risks associated with some currently available drugs with side effects comparable to or more severe than leflunomide (e.g., the oncolytics) seem to be generally well managed in clinical practice. Evidence cited the November 7 memo would argue for a careful consideration of the full range of risk management options before market withdrawal.

Although not a basis for my conclusions below, I feel it important to comment on the “Ethical Considerations” section of the November 7, 2002 memo. Efforts to manage the known risks of drugs are not “experiments” even when the effectiveness of these risk management strategies has not been thoroughly or rigorously tested. As no drug is free of risk, every drug approved by the Agency is accompanied by information to physicians on how to manage the known risks associated with the product based on available evidence. The limitations of the clinical trials to completely assess at the time of approval all of the comorbidities, coprescriptions and relatively rare adverse events that might occur or be observed once a drug is in general use are well described. Efforts to minimize the risks of therapy and to understand problems that may arise post-marketing are not “experiments,” as indicated in the memo, but are ethical and humane approaches to evaluate and ensure the best and most appropriate use of drugs. Current efforts to communicate safety information and manage the risk of drugs are designed to protect patients from harm and not to conduct further clinical trials.

Conclusion:

The November 7, 2002 review acknowledges that there may be patients for whom the benefit of leflunomide exceeds the risk. I recommend that the situations where the benefits of treatment with leflunomide exceed the risks be well documented, and that

ways to ensure that the drug is reserved for these situations be explored before concluding that the drug has no clinical utility and must be withdrawn from the market. I also recommend that ways to effectively manage the risks of leflunomide therapy, including changes in its general availability and other risk management strategies, be carefully considered to ensure that the risks associated with therapy are minimized and benefits maximized.