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Lawrence Goldkind, M.D.
Deputy Director, Division of Analgesic and
Inflammatory Drug Products
Food and Drug Administration
Rockville, MD 20857

Dear Dr. Goldkind:

I have reviewed the material that you provided regarding spontaneous reports of liver injury, acute liver failure, and death in association with the use of leflunomide. These included:

1. US reported cases of acute liver failure and death
2. US reported cases of serious liver injury
3. Foreign reports of serious liver injury, acute liver failure or death

Review of the clinical case histories reveals that the majority of affected patients had been treated with multiple drugs in addition to leflunomide, and often had comorbidities, including underlying liver disease. A history of alcohol abuse was also not uncommon. In many cases insufficient clinical information is provided, particularly in the foreign reports, to fully assess potential confounding variables that could account for liver injury.

With the above as a caveat, I did utilize the Office of Drug Safety criteria to assess drug related liver injury in the seventeen US reported cases of acute liver failure and death. The clinical information is most complete for this group.

Among these patients:

1. *Unlikely* (2): Two individuals appear to have other, more likely, causes of their liver injury, namely, post-operative jaundice and cirrhosis, with esophageal varices. I would therefore consider these cases to be *"Unlikely"* related to leflunomide use.

2. *Possible (10):* Ten individuals have a history of alcohol abuse, underlying liver disease, and/or received methotrexate co-therapy. These cases would meet criteria to be considered *"Possibly"* related to leflunomide.

3. *Probable (5):* In five of the seventeen cases there were no apparent co-morbidities or other drugs conventionally associated with severe hepatoxicity. However, it should be noted that four of these individuals were taking other medications, including celecoxib, hydroxychloroquine and amiodarone. In addition, one of these patients was administered leflunomide 100mg/ d for 87 days prior to the onset of liver failure. Using the Office of Drug Safety criteria, one cannot exclude a causal relationship to leflunomide, and, therefore, these cases would meet criteria as *"Probably"* related to leflunomide therapy.

I have attached a table summarizing these cases and my assessment of drug related injury. I have also carefully reviewed the other US reported cases of serious liver injury and the Foreign reports of serious liver injury, acute liver failure or death. I have not provided specific assessments of drug-related toxicity for these cases since there is generally less clinical detail provided, particularly with respect to co-morbidities and other drug treatments. I can attempt to do so if you think it is important. In general, as in the seventeen cases described above, these clinical case histories are commonly complicated by polypharmacy and co-morbidity. Therefore, given the presence of confounding variables, the lack of clinical detail, as well as the possibility that the reported events were due to chance alone, one cannot attribute the *"Probable"* cause of hepatic toxicity to leflunomide in the vast majority these reports.

Finally, to place these reports in context, it should be noted that leflunomide can be highly effective in the treatment of difficult inflammatory arthritis and, for many individuals, is the mainstay of their DMARD therapy. As we know, it is difficult to properly assess the reported adverse events without information regarding the numbers of individuals treated with leflunomide worldwide, including an estimate of the number of patient/years of exposure. Such assessment must therefore be considered in the context of the overall risk-benefit of leflunomide treatment, which based upon the clinical information published to date, does not appear to differ from other DMARD treatments.

I appreciate the opportunity to review the case reports. Please let me know if you would like additional information or clarification.

Sincerely,

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Steven B. Abramson, M.D.

cc: Dr. L.Simon