Center For Drug Evaluation
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Office of
Regulatory Policy

March 28, 2002

Tommy Thompson
Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

Dear Secretary Thompson:

Public Citizen, representing 135,000 consumers nationwide, hereby petitions the Food and Drug Administration (FDA) pursuant to the Federal Food, Drug and Cosmetic Act 21, U.S.C. Section 355(e)(3), and C.F.R. 10.30, to immediately remove from the market Arava (leflunomide; Aventis), a drug for the treatment of rheumatoid arthritis. From when it was first marketed in late September 1998 through September 2001, Arava has been associated with at least 130 severe hepatic reactions including 56 hospitalizations and 22 deaths, two of whom were patients in their twenties. For 12 of these deaths, leflunomide-induced liver toxicity appears to be the most plausible explanation. Similar serious reactions have caused the European Agency for the Evaluation of Medicinal Products (EMEA) to issue an urgent warning to patients and physicians concerning the potential causal relationship of leflunomide to severe liver injury, including death.

Methotrexate, an equally or more effective alternative to leflunomide (Table 12), is widely used to treat many patients with rheumatoid arthritis. It is thus important to compare the number of serious adverse reactions of the two drugs and to put this in the context of their relative number of prescriptions. From the end of September 1998, when leflunomide was first marketed in the U.S, through the third quarter of 2001--the interval during which we have obtained adverse reaction reports on the two drugs--there were approximately 1.5 million prescriptions filled for leflunomide and 8.3 million for the oral version of methotrexate in the U.S.

In other words, there were approximately 5.5 times more prescriptions filled for methotrexate than for leflunomide during this interval. However, as shown in table 1, below, there were six times more reports of fatal liver toxicity with leflunomide than with methotrexate (12 vs. 2), 13 times more reports of hypertension than for methotrexate (38 vs. 3) and, for the life-threatening autoimmune disease, Stevens-Johnson

Syndrome, there were 12 cases with leflunomide and none with methotrexate. For all of these serious adverse reactions, therefore, the toxicity of leflunomide is clearly greater than that of methotrexate, especially since there were 5.5 times more prescriptions filled for methotrexate than for leflunomide during the interval.

Table 1. Serious adverse effects reports for leflunomide and methotrexate (AERS database)

Adverse Effects	Leflunomide	Methotrexate
Liver toxicity fatalities	12	2
Hypertension	38	3
Autoimmune Stevens Johnson Syndrome	12	0

We have undertaken our own analysis of available data using FDA Medical Officer reviews, Cochrane Library reviews (the most comprehensive meta-analyses available on medical issues), FDA's Arthritis Advisory Committee transcript of August 7, 1998, FDA adverse event reports (AERS), and the medical literature and have found not only many cases of severe drug-induced hepatotoxicity, but also large numbers of lymphomas as well as other hematologic, gastrointestinal, and skin reactions serious enough to cause hospitalizations and deaths, and a large number of cases of drug-induced hypertension.

Early animal studies had shown serious liver toxicity (necrosis) at doses much lower than the human dose. The first human evidence of liver toxicity appeared during the clinical trials before approval with four cases of grossly abnormal liver function test (LFT) enzymes and two patients requiring biopsies. (One patient had elevations of 39x and another 80x the upper limit of normal for the LFT.) In the most carefully conducted study that compared leflunomide with methotrexate, 7.1% of patients on leflunomide had abnormal LFTs vs. 3.3% of patients on methotrexate and 1.7% of patients on placebo. Patients on leflunomide were also more likely to withdraw from the trial due to adverse events: 22% of patients on leflunomide vs. 10% on methotrexate and 9% on placebo.[1]

Moreover, the efficacy of leflunomide on the primary outcome measure in patients with arthritis is likely inferior to methotrexate: in the placebo-controlled trial (US301), leflunomide and methotrexate were considered equally effective (41% of patients on leflunomide, 35% on methotrexate, and 19% on placebo

[1] Strand V, Cohen S, Schiff M et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Archives of Internal Medicine 1999;159:2542-50.

responding[2]) while in a much larger, comparison trial of methotrexate and leflunomide (MN302), methotrexate was significantly superior (57% response rate in those on methotrexate compared with 43% of those on leflunomide, $p \leq 0.0001$[3]). (Responders were those who met the American College of Rheumatology criteria for 20% improvement in a set of predefined criteria (ACR 20).

The accumulated data suggest that leflunomide is more toxic and lacks increased efficacy compared with methotrexate, the current standard of disease-modifying treatment for rheumatoid arthritis. Since there are, besides the NSAIDS and corticosteroids, at least eight other disease-modifying drugs available for treatment (Table 13), and since some of these are more efficacious and less toxic, leflunomide's continued use cannot be justified.

BRIEF TRIAL DESCRIPTIONS

There were three pivotal clinical trials (Phase III) submitted in support of the New Drug Application; all were randomized, two were placebo-controlled and one positive-controlled. The only data on the combination of leflunomide and methotrexate was a Phase II trial, Study F01 (trial descriptions in Table 11).

In the randomized trials mentioned above, there were important differences in LFT[4] monitoring and concomitant use of folate. Folate is important because it prevents much of the gastrointestinal and liver toxicity caused by methotrexate; thus, it is not valid to compare leflunomide with methotrexate adverse events where folate was not provided, the case with MN302. In assessing hepatotoxicity, the most weight, therefore, should be given to US301, which, in addition to providing folate to all patients for protection against adverse events, had far superior LFT monitoring (Table 2).

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[2] John Hyde, M.D., FDA Medical Officer's Review of leflunomide, September 3, 1998, p.21.
[3] Ibid; p.33.
[4] *ALT*, AST, and ALKP are liver enzymes and *bilirubin* is a liver by-product; all are measures of liver toxicity when they escape from the liver into the bloodstream.

Table 2. LFT monitoring in pivotal clinical trials[5]

Trial	Folate use (% of pts)	Baseline LFT exclusion definition	Monitoring	Alcohol use	Action to be taken by investigator
US301	100	Persistently abnormal LFTs as defined as >2 serial elevations of AST, ALT, ALKP or bilirubin >1.2x ULN or persistently abnormal albumin	biweekly (for 6 weeks); then monthly	patients advised against	must confirm w/in 72 hr; then must conform to preset standards of action
MN301	≤10[a]	Patients with liver disease which has not resolved completely as defined by serum levels of SGOT, SGPT, ALKP, or bilirubin that are 2x ULN	biweekly (for 4 weeks); then monthly	no info	action left up to the investigator
MN302	n.a.	Liver disease which has not resolved completely as defined by serum levels of SGPT that are 2xULN	biweekly (for 4 weeks); then monthly	no warnings	action left up to the investigator

[a] folate, when used, usually added after the occurrence of an adverse event[6]

[5] John Hyde, M.D., FDA Medical Officer's Review of leflunomide, September 3, 1998, p.60; http://www.fda.gov/cder/foi/nda/98/20905_arava.htm

[6] Arthritis Advisory Committee Transcript for Leflunomide, FDA, CDER, August 7, 1998, p.59.

SAFETY

1. Hepatotoxicity

A. Animal Data

i. Dog: Mean levels of *ALT* and *bilirubin*[4] were both significantly increased in all three treated groups of male dogs at exposures of only 1/5 to 1/3 that of humans.[7] No other data were available in the review.

ii. Rat: Centrilobular necrosis (pathologic destruction of liver cells) was seen in both male and female rats at levels of only 1/5 to 1/2 that of human exposure. The pharmacology reviewer warned of the potential for liver toxicity in people taking leflunomide chronically "based on the incidences of necrosis in the liver" and further cautioned that, based on the animal findings, "Liver is the target organ of toxicity as characterized by the histological changes and the abnormality in the transaminase [LFT] activity."[8]

Liver toxicity was thought to be due, in part, to the fact that 60-77% of the administered drug was "irreversibly" bound in rat liver, a finding predicted to be especially worrisome after chronic administration.[9] Because of high drug levels in *skin and liver*, the reviewer presciently cautioned that "**Toxicity of Leflunomide in these organs needs to be closely evaluated**." (bolding by pharmacology reviewer)[10]

B. Clinical Trial Data

The major focus of the Medical Officer's Safety Review was also LFT abnormalities. Liver toxicity covered 10 pages of his review vs. less than one to two pages for each of the other potential safety problems. The most reliable liver function data came, as mentioned above, from Study US301 because of more frequent monitoring, mandatory guidelines to follow when LFT elevations occurred, and because methotrexate patients were all taking folate. The subset of patients who had normal LFT levels at baseline that subsequently rose to >3x ULN during treatment is given in Table 3.

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[7] Asoke Mukherjee, Ph.D., FDA Pharmacology Review of leflunomide, August 26, 1998, p.14.
[3] Ibid; p.31.
[9] Ibid; p.79.
[10] Ibid; p.61.

Table 3. LFT: % above 3x upper limit of normal in Study US301[11]

LFT	Leflunomide	Methotrexate	Placebo
AST	2.2%	0.5%	1.7%
ALT	4.4%	2.7%	2.5%
ALKP	0%	0%	0%

In both US301 and MN302, LFT elevations were more likely to revert to normal in methotrexate-treated than in leflunomide-treated patients (Table 4). Leflunomide-treated patients were also more likely to discontinue treatment due to LFT abnormalities (3.4% vs. 1.1% for methotrexate).[12]

Table 4. Frequency of reversal (from >3x ULN) of LFT elevations*

	Study US301			Study MN302	
LFT	leflunomide	Methotrexate	Placebo	Leflunomide	Methotrexate
AST	4/4; 100%	1/1; 100%	2/2; 100%	4/7; 57%	29/29; 100%
ALT	7/8; 88%	5/5; 100%	3/3; 100%	9/13; 69%	73/83; 88%

*Percent of patients who had LFT >3x ULN that returned to normal by endpoint of study or at follow-up.[13]

Gastrointestinal adverse events, including liver toxicity, were the major reason for withdrawals in patients on leflunomide. For study US301, abnormal LFTs were the most frequent reason for withdrawal (Table 5). After subtracting the placebo rate, the percent of patients who dropped out because of abnormal LFTs was 3.4-fold higher in patients taking leflunomide than those taking methotrexate (5.4% vs. 1.6%).

Table 5. Trial US301 withdrawal rates[14]

Adverse event	LEF	MTX	Placebo
LFT abnormal	7.1%	3.3%	1.7%
Diarrhea	2.7%	0.0%	1.7%
Nausea	1.6%	0.5%	0.0%
GI bleeding	1.1%	0.0%	0.0%

Liver toxicity also increased significantly when leflunomide was added to the drug regimen of patients who were already on methotrexate and did not have LFT abnormalities. In study F01, the only study to examine this question, 30 such patients had leflunomide added for a period of 6 months. While taking both drugs, 57% had LFT elevations ≥1.2 ULN (Table 6) whereas only 11% to 13%

[11] John Hyde, M.D., FDA Medical Officer's Review of leflunomide, September 3, 1998, p.62.
[12] Ibid; p.64.
[13] Ibid., pp.65-66.
[14] Laura Lu, Ph.D., FDA Statistical Review of leflunomide, July 10, 1998, p.7.

fell into this category when leflunomide was used alone. Three patients met ACR criteria for liver biopsy (10% of the total) even though they had had normal liver enzyme levels when receiving methotrexate alone. Although some of this safety information is in the label, it is buried under a section titled "Hepatotoxic Drugs" in such a way that neither physicians, nor patients are likely to see it.

Table 6. AST elevations in patients taking methotrexate and leflunomide Study F01 (n=30)[15]

	Affected	Resolution
>1.2x ULN	17 (57%)	
>1.2 to ≤2x ULN	7 (23%)	no data
2-3x increase	5 (17%)	2 resolved with continuation 3 resolved with discontinuation
>3x ULN	5 (17%)	5 resolved with discontinuation

The temptation to combine leflunomide with methotrexate holds many dangers: recently a patient on both drugs was found on biopsy to have severe liver damage while having normal values for LFTs.[16] This means it will not always be possible to rely on LFT monitoring, a particularly dangerous situation.

C. Post-marketing Adverse Events (AERS data base)
From the end of September 1998 (launch) through September 2001, there were 130 serious hepatic reactions for which leflunomide was listed as the primary suspect. Included in this number were 22 deaths due to hepatic failure, hepatic necrosis, and/or cirrhosis. Confounding factors were present in some of the cases, but our analysis of the data indicated that in 12 of the 24 deaths, leflunomide appeared to be the causative agent (none of the 12 was taking methotrexate) (Table 7). Two of the 12 were in their twenties. Over this same time period, there were 7 deaths involving liver toxicity for which methotrexate was listed as primary suspect but in only two cases did the drug appear to be the causative agent.

Taking into consideration the number of prescriptions filled for the drugs during this time period, the rate of reported deaths from liver toxicity from leflunomide was 12 deaths per 1.5 million prescriptions filled or 8 liver deaths per million prescriptions. For methotrexate, the rate was 2 deaths per 8.3 million prescriptions filled or 0.24 liver deaths per million prescriptions, a rate 1/33 as high as leflunomide. There are, according to the FDA, more reports filed in the first three years of a drug's marketing than subsequently but this effect, for these first three years of leflunomide's marketing, could at best account for a three-fold, not a thirty-three fold difference in the rate of reports of liver toxicity.
(Br Med J 1987;294(6565):147-50.)

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[15] John Hyde, M.D., FDA Medical Officer's review of leflunomide, September 3, 1998, p.50
[16] Weinblatt ME, Dixon JA, Falchuk KR. Serious liver disease in a patient receiving methotrexate and leflunomide. Arthritis & Rheumatism 2000;43:2609-2613.

Table 7. Deaths due to liver toxicity for which leflunomide appears to be the causative agent

Age	Gender	Liver Toxicity
23	F	Hepatic Failure
24	M	Hepatotoxicity
34	F	Hepatitis
35	F	Hepatic Necrosis
48	M	Hepatic Failure
58	F	Hepatic Failure
64	F	Hepatic Failure
66	F	Hepatic Necrosis
68	F	Hepatic Failure
73	F	Hepatic Failure
74	F	Hepatic Failure
Unknown	F	Hepatic Failure

2. Lymphoma

Leflunomide blocks the synthesis of pyridine nucleotides, building blocks needed for DNA synthesis, repair and cell division. As a result, any rapidly dividing cells are particularly sensitive to growth suppression by this drug, e.g., bone marrow, buccal (cheek), intestinal, and fetal cells. In the bone marrow, leflunomide suppresses lymphoid (T) cell multiplication and since, "The T cell is the primary cell thought to be responsible for direct recognition and killing of tumor cells," patients taking immunosuppressant drugs are left with compromised immune defense putting them at increased risk for lymphoma.[17]

Lymphoma development has been so common after drug-induced immunosuppression (such as required after organ transplantation to prevent tissue rejection), that a new disease term has been coined: "Post-Transplant Lymphoproliferative Disorder."[18] The methotrexate black-box label contains a warning about the possible occurrence of malignant lymphomas.

A. Animal Data

A mouse model has demonstrated that leflunomide can cause lymphomas in a mammalian species: in life-time testing in mice, the incidence of malignant lymphoma was doubled in males[19] with exposures as low as 1.7x that of humans (label; based on AUC); however, mice were exposed to only 1% of human drug

[17] Merck Manual; 17th ed. p.982. Beers MH, Berkow R, eds. Merck Research Labs, 1999, Whitehouse Station, N.J.

[18] Rapamycin may prevent post-transplant lymphoma. Journal of the National Cancer Institute 2001;93:1519.

[19] Asoke Mukherjee, Ph.D., FDA Pharmacology Review of leflunomide, August 26, 1998, p.44.

levels, if one bases the comparison on the maximum concentration in the blood (Cmax).[20]

The drug maker did tests for genotoxicity on the parent drug (even though it is present at such low concentrations in plasma as to be immeasurable): these tests were negative. However, they did no tests on the major active metabolite (which is what one actually measures in plasma and is present at high levels for many weeks). Interestingly, one of the minor metabolites, trifluoromethyl aniline, was a potent genotoxin (caused DNA damage in several tests) and thus is potentially capable of causing tumors.

B. Clinical Trial Data
Phase III trials, US301 and MN302, had one patient each who developed lymphoma which the investigators ascribed as "related to leflunomide administration",[21], a recognition of leflunomide's neoplastic potential. A third patient in study YU205 (a Phase II trial[22]) was diagnosed with lymphocytic leukemia, assessed by the investigator as "not related" but without any substantiating data being present in the review. Against these two cases of lymphoma in patients on leflunomide; there was one case in a patient on methotrexate, an expected finding (black-box warning in the label). Similar numbers of patients were treated with each drug in the pivotal Phase III trials (816 on leflunomide vs. 681 on methotrexate).[23]

C. Post-marketing Adverse Events (AERS data base)
From the end of September 1998 (launch) through September 2001, there were *9 cases* of lymphoma reported to the FDA: two required hospitalization and two others died. In this same time span, there were *two cases* of lymphoma in patients on oral methotrexate, a known adverse event (one died). The lymphoma cases provide further strong evidence that leflunomide's immunosuppressive properties, like those of methotrexate, place patients at risk for this malignancy. Yet, the label merely states that, "There is a potential for immunosuppression with ARAVA," a not very helpful comment. (None of the reported lymphoma patients appeared to be taking both drugs.)

The FDA's "Guidance for Industry"[24] states that, ". . . malignancies (i.e., lymphomas) are a known risk of long-term, nonselective immunosuppression used for treatment of graft recipients" and, by extension, a risk for patients with rheumatoid arthritis who are taking immunosuppressive drugs. It is telling that lymphomas may occur at least as often with leflunomide treatment as with

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[20] Ibid; p.48.
[21] John Hyde, M.D., FDA Medical Officer's Review of leflunomide, September 3, 1998, p.74.
[22] YU205 was an 18-month extension of two Phase II dose range-finding trials, YU203 and YU204. Veneeta Tandon, Ph.D., FDA Clinical Pharmacology review of leflunomide, July 15, 1998; p.22.
[23] Laura Lu, Ph.D., FDA Statistical Review of leflunomide, July 10, 1998, pp.4, 10, 14.
[24] Guidance for Industry; Clinical development programs for drugs, devices, and biological products for the treatment of rheumatoid arthritis. February 1999; p.12.

methotrexate and inexcusable that there is no warning for patients, since stopping therapy can reverse the cancer, if caught early.[25,26]

3. Pregnancy

The label begins with a black-box warning not to become pregnant while on this drug. As mentioned above, leflunomide blocks the synthesis of a basic building block for nucleic acid synthesis. Thus, any actively dividing cells are especially sensitive to its effects. These would include most cells in a developing embryo as well as sperm development in the testes.

A. Animal Data

Leflunomide is a potent teratogen in animals: even the sponsor concluded that leflunomide was teratogenic to rats at only 1/10 the maximum clinical exposure.[27] This high potency is one reason why the lack of data on the washout procedure is so critical (see page 14). The committee felt that without benefit of data from a clinical trial demonstrating the true efficacy of adsorbents in removing active drug, there was a great potential for fetal harm. Rats exposed during the period of organogenesis had embryos with serious fetal malformations in the brain (hydrocephalus), the eyes (anophthalmic or microphthalmia), and the cervical vertebral column.

Dogs had "testicular atrophy . . . at *all doses* [exposures were 0.5, 1.5, and 4.5x that of humans based on surface area; italics added] . . .[this] needs to be addressed in the reproductive safety of the label."[28] This has not been done: the label does not provide information on testicular toxicity but merely suggests that men undergo an 11-day washout with cholestyramine prior to attempting to conceive, even though there are no data showing this procedure to be effective.

B. Post-Marketing Adverse Events (AERS data base)

We searched the AERS data base for cases of reproductive toxicity occurring between the end of September 1998 through September 2001, looking at all cases where leflunomide was listed as the primary suspect responsible for the observed toxicity. Although the leflunomide label begins with a black-box warning against becoming pregnant, there were at least 34 reports of adverse reactions relating to complications of maternal exposure in the AERS database, implying either that the label is not being read or that the wash-out is not effective. During this same period for oral methotrexate, there were no adverse events related to pregnancy for which methotrexate was considered the primary suspect.

The leflunomide label states, under "Use in Women of Childbearing Potential," that human plasma levels of less than 0.02 ug/ml "are expected to have minimal risk based on available animal data" yet the drug company sponsor stated that

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[25] John Hyde, M.D., FDA Medical Officer's review of leflunomide, September 3, 1998, p.74.
[26] Label for methotrexate.
[27] FDA Reproductive Toxicity Assessment Committee report; submitted July 1998.
[28] Asoke Mukherjee, Ph.D., FDA Pharmacology Review of leflunomide, August 26, 1998, p.16.

"These animal toxicology studies do not provide a safety margin for leflunomide in terms of plasma levels, since the half-life of the active metabolite is longer and clearance is slower in humans compared to animals."[29] We don't know what a safe level is or how to achieve it.

4. Hypertension

A. Clinical Trial Data

Hypertension was defined as systolic blood pressure ≥160 mm and/or diastolic blood pressure ≥90 mm. Both the overall rate and the new onset rate were highest in the leflunomide patients.[30]

Table 8. Hypertension in pivotal clinical trials

	Leflunomide	Methotrexate	Sulfasalazine	Placebo
Overall incidence	8.9%	2.7%	3.8%	4.3%
New onset	1.6%	0.7%	0.0%	0.5%

However, when new onset hypertension was calculated taking into account duration of exposure (rate/1000 patient-years exposure), no significant differences emerged:

leflunomide 0.6
methotrexate 0.5
sulfasalazine 0.0
placebo 0.4

B. Post-marketing Adverse Events

Our analysis of the AERS database from the end of September 1998 through September 2001 showed 38 cases of hypertension where leflunomide was listed as the primary suspect. Of these, 22 patients were hospitalized and 2 died.

Table 9. Leflunomide hypertension cases (AERS database)

Type	Number of cases	Outcomes
Hypertension (not defined)	20	13 hospitalized
Hypertension aggravated	17	8 hospitalized & 2 deaths
Malignant hypertension	1	1 hospitalized
Hypertension (total cases)	38	

[29] Advisory Committee Transcript for leflunomide; August 7, 1998; p.18.
[30] John Hyde, M.D., FDA Medical Officer's review of leflunomide, September 3, 1998, p.57-60.

Our analysis of the database for oral methotrexate over the same time span showed that there was only one patient for whom methotrexate was the primary suspect for hypertension.

Table 10. Methotrexate hypertension cases (AERS database)

Type	Number of cases	Outcomes
Hypertension (not defined)	1	1 hospitalized

Thus, the apparent incidence of hypertension was much higher in patients taking leflunomide. In spite of the accumulating evidence of risk, the label makes no mention of hypertension as a post-marketing adverse reaction. This lack of information leaves physicians and patients unaware of the dangers.

5. Other adverse events seen post-approval

A. Hematologic

For leflunomide, there were 44 cases of thrombocytopenia (low platelet levels), 24 cases of pancytopenia (low levels of all types of blood cells), and 8 cases of both together in the AERS database. Of this total of 76 cases, there were 32 hospitalizations and 17 deaths. In addition, one case of severe pancytopenia has been reported in the literature.[31] The French government was so concerned about hematologic toxicity that they have recommended a blood cell count before treatment, every 2 weeks during the first 6 months and every 8 weeks thereafter.[32] The only advice present in the U.S. label is targeted at patients who were on other immunosuppressive agents to use leflunomide "with caution" and obtain "frequent clinical and hematological monitoring". The AERS database for oral methotrexate as primary suspect listed 29 cases of pancytopenia and thrombocytopenia that were responsible for 12 hospitalizations and 14 deaths.

B. Gastrointestinal

Diarrhea occurred more than twice as often in leflunomide-treated than in methotrexate-treated patients in the active-controlled trial (22% vs.10%); the rates were 27% vs. 19% in the two placebo-controlled trials.[33] In post-marketing reports, there were four cases of hemorrhagic diarrhea as well as 98 additional cases of diarrhea serious enough to be reported to the FDA; of these, 52 required hospitalization and 11 died. Compared to this, there were two cases of diarrhea reported for which methotrexate was the primary suspect (one patient was hospitalized and one died).

C. Dermatologic

Twelve cases of Stevens-Johnson Syndrome were reported to the FDA post-approval which included three deaths (one a 22-year-old) and 8 hospitalizations. There is also a published account of two cases of leucocytoclastic vasculitis

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[31] Auer J, Hinterreiter M, Allinger S. et al. Severe pancytopenia after leflunomide in rheumatoid arthritis. Acta Med Austriaca 2000;27:131.

[32] The Editors, Leflunomide and rheumatoid arthritis. Prescrire International 2001;10:36-39.

[33] John Hyde, M.D., FDA Medical Officer's review of leflunomide; September 3, 1998, p.80.

resulting in death; these deaths were stated to have occurred in a placebo-controlled phase III trial comparing leflunomide with methotrexate.[34] Since the Medical Officer's review does not mention these cases, one assumes that they were not reported to the FDA. An additional case of vasculitis in a patient on leflunomide was recently published.[35] There were no cases in the database where methotrexate was considered the primary suspect for Stevens-Johnson Syndrome over this time period.

D. Weight loss

The Medical Officer expressed "concern" over weight loss in patients on leflunomide based on data from a 6-month dose range-finding study. In the active controlled trial, those taking leflunomide were almost 3x as likely to have a ≥10% weight loss as those taking methotrexate (9.6% vs. 3.3%).[36] Data from the combined New Drug Application database which showed that 2% of patients on leflunomide, 1.3% on methotrexate, and 0.4% on placebo had weight loss as an adverse event.[37]

Since approval (September 1998) through September 2001, there have been 60 adverse event reports listing decreased weight as an adverse event with leflunomide as the primary suspect. A recent clinical study designed to examine this possible adverse effect found significant weight loss in 5 of 70 patients on leflunomide with losses ranging from 19 to 53 pounds (14% to 26% reduction from baseline) with no other explanation. These authors proposed weight loss as a more common adverse event than currently recognized.[38] They hypothesized that leflunomide interferes with oxidative phosphorylation in the mitochondria (a weight loss mechanism). Further support for this idea comes from a study on dihydroorotate dehydrogenase, the enzyme inhibited by leflunomide. Those authors were able to show that when leflunomide was present, dihydroorotate dehydrogenase-dependent oxygen consumption was abolished.[39]

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[34] Bruyn GAW, Griep EN, Korff K-J. Leflunomide for active rheumatoid arthritis. The Lancet 1999;353:1883.

[35] Holm EA, Balslev E, Jemec GB. Vasculitis occurring during leflunomide therapy. Dermatology 2001;203:258-9.

[36] John Hyde, M.D., FDA Medical Officer's review of leflunomide, September 3, 1998; Appendix Table 4.

[37] Ibid; p.80.

[38] Coblyn JS, Shadick N, Helfgott S. Leflunomide-associated weight loss in rheumatoid arthritis. Arthritis & Rheumatism 2001;44:1048-1051.

[39] Loffler M, Jockel J, Schuster G et al. Dihydroorotat-ubiquinone oxidoreductase links mitochondria in the biosynthesis of pyrimidine nucleotides. Molecular and Cellular Biochemistry 1997;174:125-129.

PROBLEMS CONTRIBUTING TO TOXICITY

1. Long half-life

Leflunomide is a pro-drug; the parent drug is essentially non-detectable in plasma since it is rapidly converted to an active metabolite, A771726. The half-life of the active metabolite is about two weeks (although there is great variability between individuals with the half-life ranging from 6 to 40 days at a dose of 25 mg/day)[40] or 96 days in a population study.[41] Since steady state plasma drug levels, on average, are not achieved for 10 to 12 weeks, it would be expected to take that long for it to disappear. Nevertheless, the label suggests that women who desire to have children should allow *two drug-free years* before attempting to conceive, implying that there are body depots where the drug remains for many months. On the other hand, the half-life of methotrexate is three to ten hours so it would achieve steady state between one and 2.5 days.

A. Animal Data

No data on half-life were included in the NDA review; some pharmacokinetic data were redacted and previous reviews were not released.

B. Clinical Data

The Clinical Pharmacology Reviewer found several factors affected leflunomide plasma drug levels: *gender* (the blood level, as an average in all women, was 31 ug/ml vs. an average of 20 ug/ml in men), *age* (for women, levels were 23 ug/ml (<46 years) increasing to 46 ug/ml (>65 years)[42], and *smoking* (smokers had lower blood levels). Only smoking is mentioned in the label, although elderly women are exposed to a doubling of plasma drug levels (compared to those under 46).

2. Lack of proven wash-out procedure

Since the active drug has an extremely long half-life, there needs to be some way to remove it in case of an adverse event or pregnancy, where it could injure the developing fetus. Otherwise, even long after patients stop using the drug, significant amounts will persist in the body. Two binding agents, cholestyramine and charcoal, were tested, neither under clinically relevant conditions such as a patient would likely face.

The effectiveness of cholestyramine (a non-absorbed binding agent in the gastrointestinal tract) was tested only after <u>*one 20 mg dose*</u> as opposed to studying patients who had been taking the drug long enough to reach steady state levels (10-12 weeks). Since plasma drug levels on the first day of dosing are much lower and tissue pools have not been filled, it is clearly much simpler at that point to lower plasma drug levels. For example, on day one, the maximal drug concentration (Cmax) was 8.5 ug/ml but reached 63 ug/ml at steady state,

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[40] Veneeta Tandon, Ph.D., Clinical Pharmacology Review of leflunomide, July 15, 1998, p.20.
[41] Brent RL. Teratogen Update: reproductive risks of leflunomide. Teratology 2001;63:106-112.
[42] Vaneeta Tandon, Ph.D., Clinical Pharmacology Review of leflunomide, July 15, 1998, p.23.

an increase of 7.4-fold.[43] Clearly, drug removal at steady state would require a much more rigorous procedure, especially with apparent tight binding to liver tissue. [The figure showing plasma drug level data after cholestyramine treatment was wrongly redacted from the Clinical Pharmacology review; as a result, one of the most important pieces of information relating to human safety was removed from public view.]

Charcoal (another unabsorbed binding agent) was a second method tested to remove plasma drug; however, this trial, again, involved giving *one-100 mg dose to one healthy subject* followed 5 to 6 days later with three doses of charcoal. The same criticism applies to this study as the one for cholestyramine above concerning single vs. steady state dosing; extending a result from one healthy person to an entire population of patients for something this important is unconscionable.

EFFICACY

The definition of a responder in the clinical trials was someone who showed 20% improvement in both swollen and tender joint counts and 20% improvement in 3 of 5 additional measures (ACR 20): 1) patient global assessment, 2) physician global assessment, 3) Modified Health Assessment Questionnaire or standard Health Assessment Questionnaire, 4) pain intensity and 5) erythrocyte sedimentation rate or C-reactive protein level. Other than number five, these are subjective endpoints.

Table 11. Clinical Trials

Trial	Study arms	Number of patients	Duration
PHASE III PIVOTAL TRIALS (double-blind, randomized)			
US 301[44]	Leflunomide Methotrexate Placebo	182 182 118	1 year
MN301[45]	Leflunomide Sulfasalazine Placebo	133 133 92	6 months
MN302[46]	Leflunomide Methotrexate	501 498	1 year
PHASE II TRIAL (open label)			
F01[47]	Leflunomide + Methotrexate	30	6 months

US: U.S. trial; MN: multinational trial

[43] Ibid; p.20.
[44] John Hyde, M.D., FDA Medical Officer's Review of leflunomide, September 3, 1998, p.19.
[45] Ibid; p.25.
[46] Ibid; p.32.
[47] Ibid; p.50.

Table 12. Primary efficacy end point (ACR 20) for randomized clinical trials

Trial	Responders (%)	Statistical significance*	Duration
US 301	Leflunomide (41%) Methotrexate (35%) Placebo (19%)	Leflunomide vs. Methotrexate (p=0.24)[48]	1 year
MN 301	Leflunomide (49%) Sulfasalazine (45%) Placebo (29%)	Leflunomide vs. Sulfasalazine (p=0.54)[49]	6 months
MN 302	Leflunomide (43%) Methotrexate (57%)	Leflunomide vs. Methotrexate p<0.0001[50]	1 year

*for comparison between the active treatments

"Study US301 showed that LEF and MTX were statistically equivalent" according to the FDA reviewer,[51] a comment echoed by the trial's authors.[52] However, the reviewer noted that in another study (MN302) methotrexate was "statistically superior to LEF," a finding stated by the trial's investigators as well.[53]

The third pivotal trial (MN301) was small (133/group for sulfasalazine and leflunomide and short (6 month); this study showed similar efficacy between the two active treatment groups. However, the authors admitted that, "long-term observations in large numbers of patients will be needed to ensure that there are no unexpected late or cumulative effects from leflunomide, and that benefit is sustained."[54]

In summary, leflunomide was less effective than methotrexate in the largest trial, and in the smaller trials, was considered equivalent to methotrexate and sulfasalazine.

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[48] Calculated from EpiInfo2000.
[49] Ibid.
[50] John Hyde, M.D., FDA Medical Officer's Review of leflunomide, September 3, 1998, p.33.
[51] Laura Lu, Ph.D., FDA Statistical Review of leflunomide, July 10, 1998, p.24.
[52] Strand V, Cohen S, Schiff M et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Archives of Internal Medicine 1999;159:2542-50.
[53] Emery P, Breedveld FC, Lemmel EM et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. Rheumatology 2000;39:655-665.
[54] Smolen JS, Kalden JR, Scott DL et al. Efficacy and safety of leflunomide compared with placebo and sulfasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. The Lancet 1999;353:259-66.

ALTERNATIVES TO LEFLUNOMIDE

Patients with rheumatoid arthritis have a number of treatment options. The Merck Manual lists six classes of treatments for rheumatoid arthritis including[55]:

1) Rest and nutrition (for acute attacks)
2) Nonsteroidal anti-inflammatory drugs and salicylates
3) Slow-acting or potentially disease-modifying drugs
   - Gold
   - Hydroxychloroquine
   - Sulfasalazine
   - Penicillamine
   - Combinations of slow-acting drugs
4) Corticosteroids
5) Cytotoxic or immunosuppressive drugs
   - Methotrexate
   - Azathioprine
   - Cyclosporine
   - Etanercept
6) Exercise, physiotherapy, and surgery

Reviews of the drugs in groups 3, 4, and 5 (except for Etanercept) are available in the Cochrane Library[56] (Table 13). There is no review of leflunomide.

Table 13 outlines a number of choices available for treating rheumatoid arthritis (besides NSAIDS and leflunomide) for which enough studies exist to have been reviewed by the prestigious Cochrane Group. Some with high toxicity are used short-term. Methotrexate has the best overall profile with high efficacy and relatively low toxicity at the doses used for rheumatoid arthritis.

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[55] The Merck Manual, 17th edition, pp.419-22. Beers MH, Berkow R, eds. Merck Research Labs, 1999, Whitehouse Station, N.J.

[56] http://www.update-software.com/cochrane/

Table 13. Drug treatments for rheumatoid arthritis (in addition to NSAIDS and leflunomide) as evaluated by Cochrane Library meta-analysis

Drug	Efficacy	Toxicity
Injectable gold	Short-term benefit	serious
Hydroxychloroquine	Moderate	low
Sulfasalazine	Moderate	high prevalence; most non-threatening & limited
Penicillamine	Moderate	high
Corticosteroids	Comparable to aspirin or chloroquine	not addressed in this review
Methotrexate	High	raised LFTs in one study
Azathioprine	Moderate	higher and more serious than other drug-modifying antirheumatic drugs (DMARDS)
Cyclosporine	Short-term important benefit in patients with progressive rheumatoid arthritis	2 to 5x increase vs. placebo in headaches, tremor, dyspepsis, nausea, paresthesia
Etanercept	Protocol only; no data available	no data

The medical journal *Prescrire International* publishes excellent summaries of the available literature on pharmaceutical drugs. Their comprehensive analysis of leflunomide and other drugs for rheumatoid arthritis concluded with, ". . . leflunomide appears to be less effective than methotrexate; and it has been associated with more severe adverse events than methotrexate or sulfasalazine . . .". Furthermore, "Leflunomide provides no clinically tangible advantage in the management of patients with rheumatoid arthritis who require treatment with a disease modifying drug. When long-term treatment with such a drug is warranted, methotrexate remains the first-choice option if maximal efficacy is sought, while antimalarials [hydroxychloroquine] and oral sulfasalazine have fewer adverse effects."[57] This conclusion has now been put into sharper focus with the accumulating list of serious adverse event reports being reported to the FDA.

LACK OF EFFECTIVENESS IN CHANGING LABELING

The FDA's Drug Risk Assessment Group along with individuals from medical schools and health care organizations has analyzed the consequences of label changes necessitated when adverse health effects showed up after marketing. Their data clearly showed that black-box warnings and "Dear Health Care

[57] The Editors, Leflunomide and rheumatoid arthritis. Prescrire 2001;10:36-39.

Professional" letters had little or no effect.[58,59] They concluded that more effective methods needed to be developed and tested to protect patients. As a result, it is extremely unlikely (as was the case with cisapride and troglitazone) that letters or label changes would stem the number and severity of the adverse events occurring with leflunomide, especially when in conflict with aggressive marketing.

CONCLUSIONS

Leflunomide offers no advantages to patients with rheumatoid arthritis since it lacks any increased efficacy and appears to pose an increased likelihood of serious adverse events such as liver toxicity when compared to methotrexate, the current gold standard. The extremely long half-life from which there is no proven escape is another deterrent to use. "Dear Health Care Professional" letters are not a solution; they have not been shown to work to protect patients from serious adverse events. With a variety of better drug treatments available, there is no reason to subject patients to an accumulating list of added risks; leflunomide should be promptly removed from the market.

ENVIRONMENTAL IMPACT STATEMENT

Nothing requested in this petition will have an impact on the environment.

CERTIFICATION

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,

Elizabeth Barbehenn, PhD
Research Analyst

Peter Lurie, MD, MPH
Deputy Director

Sidney M. Wolfe, MD
Director, Public Citizen's Health Research Group

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[58] Graham DJ, Drinkard CR, Shatin D, et al. Liver enzyme monitoring in patients treated with troglitazone. JAMA 2001;286:831-833.
[59] Smalley W, Shatin D, Wysowski DK, et al. Contraindicated use of cisapride. JAMA 2000;284:3036-3039.