

**Aventis Pharmaceuticals**



*Larry P. Bell, M.D.  
Senior Vice President & Head  
Global Regulatory Approvals & Marketing Support*

*Tel: (908) 231-3980  
Fax: (908) 231-4266  
E-mail: larry.bell@aventis.com*

August 8, 2002

**VIA OVERNIGHT DELIVERY**

Tommy Thompson  
Department of Health and Human Services  
200 Independence Avenue, S.W.  
Washington, D.C. 20201

Re: Arava®

Dear Secretary Thompson:

Enclosed please find the Response of Aventis Pharmaceuticals Inc. to Public Citizen Health Research Group's Petition (filed March 28, 2002) regarding Arava® (Leflunomide) Tablets.

We are simultaneously forwarding the required copies of this Response to the Dockets Management Branch of the Food and Drug Administration for filing.

Sincerely,

A handwritten signature in black ink that reads "Larry P. Bell".

Larry P. Bell, M.D.

LPB/dp  
Enclosure

Tommy Thompson  
Department of Health and Human Services  
August 8, 2002  
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cc: Janet Woodcock, M.D.  
Director, Office of the Center  
Center for Drug Evaluation and Research  
Food and Drug Administration

John Jenkins, M.D.  
Director, Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration

Jonca Bull, M.D.  
Director, Office of Drug Evaluation  
Center for Drug Evaluation and Research  
Food and Drug Administration

Lee Simon, M.D.  
Director, Office of Drug Evaluation  
Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

Dockets Management Branch  
Food and Drug Administration  
Room 1061  
5630 Fishers Lane  
Rockville, Maryland 20852

Docket No. 02P-0139

**RESPONSE OF AVENTIS PHARMACEUTICALS INC.  
TO PUBLIC CITIZEN HEALTH RESEARCH GROUP'S  
PETITION REGARDING ARAVA® (LEFLUNOMIDE) TABLETS**

**Submitted By Aventis Pharmaceuticals Inc.  
August 8, 2002**

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## Executive Summary And Introduction

Aventis Pharmaceuticals Inc. ("Aventis") submits this response to Public Citizen Health Research Group's ("HRG") March 28, 2002 Petition (the "Petition") requesting withdrawal of Arava® (leflunomide) Tablets from the market.<sup>1</sup> For the reasons discussed below, the Petition should be denied. The substantial and unique benefits of Arava® in the treatment of rheumatoid arthritis ("RA") clearly outweigh the risk of serious adverse events that may be associated with its use.

### The Petition Mischaracterizes The Data

The Petition does not present a reasoned, scientific analysis; rather, it asserts unsubstantiated conclusions that ignore publicly available data, published literature, and standard medical practice.<sup>2</sup> In particular, the Petition trivializes the severity of RA, mischaracterizes the current clinical standard for RA patient care, distorts the safety and efficacy of alternative treatments, and ignores the treatment approaches recommended by the American College of Rheumatology ("ACR"). In short, HRG presents no substantive benefit-risk analysis for Arava® -- whether alone, in comparison to alternative therapies, or relative to the increased morbidity and mortality associated with RA. As stated by Gary S. Firestein, M.D., Chair of the FDA's Arthritis Advisory Committee, in his unsolicited letter opposing the Petition: "[M]erely describing the potential toxicity of an agent in a vacuum is not only insufficient but can be misleading." See Appendix A, 6/10/02 Correspondence from Dr. Firestein to FDA.

### The Positive Benefit-Risk Profile Of Arava®

A substantive benefit-risk analysis requires objective scientific consideration of multiple factors. Among other things, one must consider the nature and severity of RA, the current standard of medical care and knowledge, the risks and benefits of other available therapies, and the efficacy and safety data associated with Arava®. A fair and balanced evaluation of the facts confirms the positive benefit-risk profile of Arava® -- and the continuing need for Arava® as an important treatment option for the many patients who suffer from this chronic, debilitating disease:

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<sup>1</sup> Aventis will refer to Arava® and leflunomide interchangeably throughout this Response.

<sup>2</sup> As demonstrated herein, HRG's certification that the Petition includes representative data unfavorable to its position is a misrepresentation. Substantial publicly available data that contradicts HRG's position has either been ignored or mischaracterized.

## 1. Nature And Severity Of Rheumatoid Arthritis

Rheumatoid arthritis is a debilitating autoimmune disease that affects more than 2 million Americans. The cause is unknown, and there is no known cure. Most patients exhibit a chronic fluctuating course of disease that can result in progressive joint destruction, deformity, disability, and, sometimes, premature death.<sup>3</sup> RA also affects other tissues and organs and results in more than 9 million physician visits and 250,000 hospitalizations per year.<sup>4</sup> It frequently affects patients in their most productive years, and the disability associated with the disease results in major economic loss to the individual and society.<sup>5</sup>

## 2. Standard Of Care And The Limitations Of Other Available Therapies

The accepted standard of care for patients with RA is aggressive, early treatment with disease-modifying antirheumatic drugs (“DMARDs”), which slow and potentially alter the course of the disease.<sup>6</sup> However, no single DMARD is effective in all patients, and secondary failures (loss of efficacy) are not uncommon. Accordingly, most patients with active RA require the progressive addition or change of treatments over time. Each of these therapies has been associated with serious and sometimes fatal adverse events. The need for alternative therapies remains the force driving recent development and approval of new treatments for RA in the last 4 years.

## 3. Clinically Proven Efficacy Of Arava®

Arava® has been shown in randomized, controlled trials to: (i) reduce the signs and symptoms of active RA; (ii) retard structural joint damage measured by radiographs; and (iii) improve physical function and health related quality of life. Arava® targets the underlying inflammatory process -- rather than just treating symptoms -- by inhibiting multiplication of T-cells believed to perpetuate the autoimmune response in RA. It is also effective in treating both early and long-standing disease, as long- and short-term therapy, and regardless of disease severity or previous exposure to other DMARDs. In clinical trials, Arava® had a faster onset of

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<sup>3</sup> Guidelines for the Management of Rheumatoid Arthritis, American College of Rheumatology Ad Hoc Committee On Clinical Guidelines (hereinafter “ACR Guidelines Update 2002”). *Arthritis Rheum*, 2002; 36(2) 328-46; Wolfe F. The burden of rheumatoid arthritis. *Am J Manag Care*. 1999; 5:S852-S859.

<sup>4</sup> ACR Guidelines Update 2002; Gabriel SE, Crowson CS, O’Fallon WM: The epidemiology of rheumatoid arthritis in Rochester, Minnesota, 1955-1985. *Arth Rheum* 1999; 42:415-20; Gabriel, S. E. The epidemiology of rheumatoid arthritis. *Rheum Dis Clin North Am*. 2001;27:269-81; Doran MF, Pond GR, Crowson CS, O’Fallon WM, Gabriel SE: Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a 40 year period. *Arthritis Rheum* 2002; 46:625-31.

<sup>5</sup> *Id.*

<sup>6</sup> ACR Guidelines Update 2002.

action and equivalent improvement in physical function and radiographic progression when compared with methotrexate, the primary comparator drug referenced by HRG. Overall, clinical trial results confirm that the efficacy of Arava® is equivalent to both methotrexate and sulfasalazine.

Because of its unique properties and the need for additional DMARD treatments, Arava® received priority review by the U.S. Food and Drug Administration (“FDA”),<sup>7</sup> and an expert Arthritis Advisory Committee convened by the FDA unanimously supported marketing approval -- based on the same clinical trials referred to by HRG. Since the New Drug Application (“NDA”) was approved in 1998, Arava® has been prescribed to more than 500,000 patients worldwide.

#### **4. The Risk Of Adverse Events Is Outweighed By The Benefits Associated With Arava® Therapy**

Throughout the Petition, HRG mischaracterizes and selectively cites clinical trial and post-marketing data, while ignoring critical information that clearly undermines its position. HRG’s superficial analysis is not a substitute for a careful and thorough benefit-risk evaluation.

The facts confirm that Arava® is an important advance in the treatment of RA and should remain available to the many thousands of individuals who benefit from use of drug. The chronic, progressive, and destructive nature of RA warrants the use of DMARDs early in the disease process. Arava® has been clinically proven to have efficacy in early and advanced disease, with rapid onset of therapeutic effect and sustained benefit during long-term therapy.

These established benefits of Arava® must be weighed against its recognized risks, in the context of other available therapies and the severity of the disease. The risk of serious<sup>8</sup> and sometimes fatal adverse events has, unfortunately, been observed with most prescription medications -- and all DMARDs, including Arava®. In fact, treatment with each available DMARD has been associated with serious adverse events. None has a safety profile clinically proven to be superior to Arava®. Specifically, the safety data from randomized controlled trials show the overall percentage of patients with adverse events who were treated with Arava® was

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<sup>7</sup> A new drug application may receive priority review if “[t]he drug product, if approved, would be a significant improvement compared to marketed products . . . in the treatment, diagnosis, or prevention of a disease.” Center for Drug Evaluation and Research, Manual of Policies and Procedures 6020.3. Priority review does not mean that less data is required to receive approval, but that, by regulation, the FDA will act on an expedited track due to the important therapeutic potential offered by the product.

<sup>8</sup> The term “serious adverse events” is defined by the Code of Federal Regulations. See *infra* footnote 94.

generally comparable to that of patients who received methotrexate and sulfasalazine. Importantly, nothing in the post-marketing experience changes the acceptable benefit-risk profile established by the controlled clinical studies.<sup>9</sup>

When weighed against the benefits of the drug, its impact on the disease course, and the limitations of other available therapies, the risks of Arava® treatment are clearly outweighed by its substantial benefits. Accordingly, the FDA and other regulatory bodies have correctly concluded that Arava® is one of the safe and effective therapies in the limited arsenal available to treat RA. Recently, the Agency for the Evaluation of Medicinal Products ("EMEA") and the Committee of Proprietary Medicinal Products ("CPMP") in Europe completed an exhaustive analysis of Arava® -- including the post-marketing and clinical trial data -- and concluded that "[t]he current benefit-risk assessment of ARAVA is positive and no change in SPC is needed" at the present time.<sup>10</sup> These conclusions continue to be supported by new data, including recent post-marketing clinical studies and surveillance reports, as well as the largest database analysis in RA patients. *See infra* subsection IV.B. The Petition does not support a contrary conclusion and, accordingly, should be denied.

\* \* \* \* \*

The balance of this Response will address these matters in greater detail." Part I will discuss the nature and severity of RA and known limitations of the available therapies. Part II describes the proven clinical efficacy of Arava®. Part III reviews the clinical trial safety data and post-marketing surveillance relating to Arava®. Part IV confirms the positive benefit-risk profile of Arava®. Finally, Part V demonstrates that the legal standard applicable to withdrawal of an NDA has not been satisfied and that the Petition should be denied.

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<sup>9</sup> When the post-marketing Arava® experience has produced an indication that there may be events not seen in clinical trials (or an increased frequency of previously observed events), Aventis has worked with the FDA to update the prescribing information and to notify physicians. Aventis is currently working with the FDA to further update the prescribing information based on post-marketing information.

<sup>10</sup> The EMEA performs administrative oversight and mobilizes scientific resources throughout Europe for medicinal products marketed in the European Union. The CPMP is a scientific standing Committee that evaluates medicinal products on behalf of the member states of the European Union and advises the European Union. The SPC is the Summary of Product Characteristics, which is analogous to prescribing information in this country.

<sup>11</sup> Aventis does not waive and expressly reserves all rights to the confidentiality of data and information contained in all submissions to the FDA relating to Arava®, including, but not limited to, the NDA and the Investigational New Drug application for Arava®. 5 U.S.C. §552(b)(4); 21 C.F.R. §§312.130, 314.430, 20.61.

## I. RHEUMATOID ARTHRITIS IS A SEVERE, DISABLING DISEASE; ALL AVAILABLE THERAPIES HAVE LIMITATIONS

HRG argues that: (i) methotrexate is the “gold standard” for the treatment of RA; (ii) methotrexate is more efficacious and safer than Arava®; and (iii) methotrexate and the other available therapies, as well as surgery, exercise, and rest, are adequate substitutes for Arava®.<sup>12</sup> These arguments minimize or ignore the severity of RA, disregard the risks of secondary failures and adverse events associated with methotrexate and other available therapies (including the recently approved biologic agents), and understate the benefits offered by Arava®.

### A. THE SEVERITY AND PREVALENCE OF RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a severe, chronic, debilitating disease where the body’s immune system loses its normal regulatory mechanisms and attacks the healthy tissue lining the joints. This leads to inflammation of the joints and destruction of the adjoining soft tissues and bone, resulting in pain and loss of physical function. Joint damage can occur in the first year of the disease process, and the probability of developing erosions or other joint damage within the first 2 years is over 70 percent.<sup>13</sup> RA is progressive, often resulting in joint deformity and physical disability, and is associated with an increased risk of premature mortality. Because RA is a systemic disease, it causes fatigue and malaise and may also damage other organs, such as the heart, lungs, spleen and skin.

Approximately 2 million persons in the United States have RA, 70 percent of whom are women. Although the onset of disease frequently occurs in the 20s and 30s, with incidence and prevalence increasing with age, RA affects all age and ethnic groups in all parts of the world. The exact cause of RA is not known, and there is no known cure.<sup>14</sup>

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<sup>12</sup> The Petition suggests that methotrexate, the most widely used DMARD on the market (used for the past 25 years and approved for RA in 1986), is the drug of choice because of physician familiarity and fewer associated adverse events than other DMARDs. However, reporting of adverse events has been shown to significantly decrease after the first two years that a drug is on the market, because, among other things, physicians tend to report adverse events less frequently once they become familiar with use of individual medications (often referred to as the “Weber” effect). Tsong, Y. Comparing reporting rates of adverse events between drugs with adjustment for year of marketing and secular trends in total reporting. *J of Biopharm Stat*, 1995; 5(1): 95-114. It is impossible to directly compare a 25-year old drug with a drug approved only 4 years ago when using spontaneous adverse event reporting as an index of safety.

<sup>13</sup> ACR Guidelines Update 2002; Fuchs HA, et al. Evidence of significant radiographic damage in rheumatoid arthritis within the first 2 years of disease. *J Rheumatol* 1989;16(5):585-591; Brook A, et al. Radiographic changes in early rheumatoid disease. *Ann Rheum Dis* 1977;36:71-73; Mottonen TT. Prediction of erosiveness and rate of development of new erosions in early rheumatoid arthritis. *Ann Rheum Dis* 1988;47:648-653; Plant MJ, et al. Measurement and prediction of radiological progression in early rheumatoid arthritis. *J Rheumatol* 1994;21(10):1808-1813. An additional study found radiographic damage in 70% of patients within 3 years. Van der Heijde DMFM, et al. Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. *Arthritis Rheum* 1992;35(1):26-34.

<sup>14</sup> Hochberg MC. Adult and juvenile rheumatoid arthritis: current epidemiologic concepts. *Epidemiol Rev* 1981; 3:27-44; Borigini MJ, et al. “Rheumatoid Arthritis. In: *Treatment of the Rheumatic Diseases: Companion to the Textbook of Rheumatology*; Weisman MH and Weinblatt ME, eds. WB Saunders Co., Phila. c1995; Allaire S, et al. The costs of rheumatoid arthritis; *PharmacoEconomics* 1994, 6;(6):513-522;

## 1. Rheumatoid Arthritis Is Associated With Significant Adverse Health Consequences

Rheumatoid arthritis is associated with significant morbidity and premature death.<sup>15</sup> In a 25-year prospective study, median life expectancy of RA patients was shortened by 4 to 7 years in males and 3 to 10 years in females.<sup>16</sup> In RA patients with severely impaired physical function, 5-year survival was 50 percent or less, a prognosis no less severe than that of patients with Stage IV Hodgkin's lymphoma or 3-vessel coronary artery disease.<sup>17</sup>

RA may result in premature death due to complications of the disease in the joints or extra-articular (non-joint) manifestations of the disease, as discussed below:

- RA can lead to an unstable cervical spine and paralysis or death. Damaged joints can become infected, leading to potential infection in the bloodstream (i.e., septicemia or sepsis), which can be fatal.<sup>18</sup>
- Extra-articular manifestations of RA may include cardiac disease caused by rheumatoid inflammation of the heart lining (pericarditis), muscle (myocarditis), or valves (endocarditis); pulmonary disease (rheumatoid lung); vasculitis; amyloidosis, which can affect the kidneys; and Felty's syndrome, which can result in life-threatening infection. In addition, RA carries an increased risk of lymphomas and serious infections, such as pneumonia or sepsis, due to suppression of normal immune responses.<sup>19</sup>
- Premature coronary artery disease associated with RA is believed to be related to the B-cell, macrophage, and T-cell effects of this autoimmune disease.<sup>20</sup>

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Goronzy J and Weyand C. Rheumatoid Arthritis, Epidemiology, Pathology, and Pathogenesis. In: Primer on the Rheumatic Diseases. Klippel JH, ed. edition 12, Arthritis Foundation, Atlanta, 2001.

<sup>15</sup> See footnote 14; Wolfe F. The burden of rheumatoid arthritis. *Am J Manag Care*. 1999; 5:S852-S859; Mikuls, TR, Saag, KG. Comorbidity in rheumatoid arthritis. *Rheum Dis Clin North Am*. 2001;27:283-303; Pincus T, et al. Premature mortality in patients with rheumatoid arthritis: evolving concepts. *Arthritis Rheum* 2001;44(6):1234-1236; Mitchell DM, et al. Survival, prognosis, and causes of death in rheumatoid arthritis. *Arthritis Rheum* 1986;29(6):706-714; Pincus T, et al. Taking mortality in rheumatoid arthritis seriously—predictive markers, socioeconomic status and comorbidity. *J Rheumatol* 1986;13(5):841-845; Scott DL, et al. Long-term outcome of treating rheumatoid arthritis: results after 20 years. *Lancet* 1987;1:1108-1111.

<sup>16</sup> Vandenbroucke JP, et al. Survival and cause of death in rheumatoid arthritis: A 25-year prospective followup. *J Rheum* 1984;11(2):158-161; Mitchell DM, et al. Survival, prognosis, and causes of death in rheumatoid arthritis. *Arthritis Rheum* 1986;29(6):706-714; Scott DL, et al. Long-term outcome of treating rheumatoid arthritis: results after 20 years. *Lancet* 1987;1:1108-1111.

<sup>17</sup> Pincus T, et al. Taking mortality in rheumatoid arthritis seriously—predictive markers, socioeconomic status and comorbidity. *J Rheumatol* 1986;13(5):841-845; Pincus T, et al. Prediction of long-term mortality in patients with rheumatoid arthritis according to simple questionnaire and joint count measures. *Ann Int Med* 1994;120(1):26-34.

<sup>18</sup> See footnote 16, Vandenbroucke; Goldenberg DL, Bacterial Arthritis In: Textbook of Rheumatology, 6<sup>th</sup> edition, Kelley WN, et al, eds., WB Saunders Co, Phila 2001; Harris ED. Clinical features of rheumatoid arthritis. In: Textbook of Rheumatology, 6<sup>th</sup> edition, Kelley WN, et al, eds., WB Saunders Co, Phila 2001.

<sup>19</sup> Borigini MJ, et al. "Rheumatoid Arthritis. In: Treatment of the Rheumatic Diseases: Companion to the Textbook of Rheumatology; Weisman MH and Weinblatt ME, eds. WB Saunders Co., Phila. c1995; Mitchell DM, et al. Survival, prognosis, and causes of death in rheumatoid arthritis. *Arthritis Rheum* 1986;29(6):706-714; Vandenbroucke JP, et al. Survival and cause of death in rheumatoid arthritis: A 25-year prospective followup. *J Rheum* 1984;11(2):158-161; Wolfe F, et al. The mortality of rheumatoid arthritis. *Arthritis Rheum* 1994;37(4):481-494; Anderson R. Rheumatoid Arthritis, Clinical and Laboratory Features. In: Primer on the Rheumatic Diseases. Klippel JH, ed. edition 12, Arthritis Foundation, Atlanta, 2001; Harris ED. Clinical features of rheumatoid arthritis. In: Textbook of Rheumatology, 6<sup>th</sup> edition, Kelley WN, et al, eds., WB Saunders Co, Phila 2001.

<sup>20</sup> Goodson N. Coronary artery disease and rheumatoid arthritis. *Current Opinion in Rheumatology* 2002; 14:115-120; Meyer O. Artherosclerosis and connective tissue diseases. *Joint Bone Spine* 2001;68:564-575; del Rincón I, et al. High incidence of cardiovascular events

In addition, other extra-articular manifestations of RA may add to the chronic debility, such as rheumatoid eye disease (which can cause blindness); inflammation of tear glands and salivary glands (called Sjogren's syndrome) with ocular and oral complications; neuropathy; inflammatory nodules under the skin (called rheumatoid nodules); fatigue; fever; and anemia.<sup>21</sup>

Few RA patients have a short disease course with spontaneous and permanent remission. Most RA patients have progressive disease over the years, with periods of worsened disease activity (called flares).<sup>22</sup> The most advanced stages of RA are characterized by debilitation due to destruction of cartilage and bone and may include bony ankylosis (fusion) of the joint, joint deformity, and extensive muscle atrophy, with inability to perform even the most simple activities of daily living.<sup>23</sup>

## **2. Rheumatoid Arthritis Is Associated With Significant Economic And Personal Consequences**

Impaired physical function associated with RA leads to decreased ability or inability to perform regular activities of daily living, work disability and reduced health-related quality of life. Work disability has been reported in 50 percent of RA patients within 10 years of onset of the disease.<sup>24</sup>

Rheumatoid arthritis accounts for over 250,000 hospitalizations and over 9 million physician visits yearly.<sup>25</sup> The costs to society have been estimated at up to \$14 billion per year.<sup>26</sup> RA patients have 3 times the direct medical care costs, twice the hospitalization rate, and 10

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in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthr Rheum* 2001;44(12):2737-2745; Manzi S, et al. Inflammation-mediated rheumatic diseases and atherosclerosis. *Ann Rheum Dis* 2000; 59:321-325.

21 Anderson R. Rheumatoid Arthritis, Clinical and Laboratory Features. In: Primer on the Rheumatic Diseases. Klippel JH, ed. edition 12, Arthritis Foundation, Atlanta, 2001; Harris ED. Clinical features of rheumatoid arthritis. In: Textbook of Rheumatology, 6<sup>th</sup> edition, Kelley WN, et al, eds., WB Saunders Co, Phila 2001.

22 *Id.*, Harris; Matteson E. Rheumatoid Arthritis, Treatment. In: Primer on the Rheumatic Diseases. Klippel JH, ed. edition 12, Arthritis Foundation, Atlanta, 2001; Pope RM. Rheumatoid arthritis: pathogenesis and early recognition. *Am J Med* 1996;100 (Supp 2A):3S-8S.

23 Steinbrocker O, et al. Therapeutic criteria in rheumatoid arthritis. *JAMA* 1949;140:659-662.

24 Felts W et al. The economic impact of the rheumatic diseases in the United States. *J Rheumatol* 1989; 16:867-884; Allaire SH, Prashker MJ, Meenan RF. The costs of rheumatoid arthritis. *Pharmaco-economics* 1994; 6:513-22; Kobelt G, Eberhardt K, Jonsson L, Jonsson B. Economic consequences of the progression of rheumatoid arthritis in Sweden. *Arthritis Rheum* 1999;42:347-56; Pugner KM, Scott DL, Holmes JW, Hieke K. The costs of rheumatoid arthritis: an international long-term view. *Semin Arthritis Rheum* 2000;29:305-20; Yelin E, Callahan LF. The economic cost and social and psychological impact of musculoskeletal conditions. *Arthritis Rheum* 1995;38:1351-62; Yelin E, Wanke LA. An assessment of the annual and long-term direct costs of rheumatoid arthritis: the impact of poor function and functional decline. *Arthritis Rheum* 1999; 42:1209-18; Yelin E. The costs of rheumatoid arthritis: absolute, incremental, and marginal estimates. *J Rheumatol* 1996;23 suppl 44:47-51.

25 *ACR Guidelines Update 2002*; Wong JB, Ramey DR, Singh G. Long-term morbidity, mortality, and economics of rheumatoid arthritis. *Arthritis Rheum* 2001;44:2746-49; van Jaarsveld CH, Jacobs JW, Schrijvers AJ, Heurkens AH, Haanen HC, Bijlsma JW. Direct cost of rheumatoid arthritis during the first six years: a cost-of-illness study. *Br J Rheumatol* 1998;37:837-47; Pincus T. The underestimated long-term medical and economic consequences of rheumatoid arthritis. *Drugs* 1995; 50 (suppl 1):1-14; Merkesdal S, Ruof J, Schoffski O, Bernitt K, Zeidler H, Mau W. Indirect medical costs in early rheumatoid arthritis: composition of and changes in indirect costs within the first three years of disease. *Arthritis Rheum* 2001; 44: 528-34.

26 Callahan L. The burden of rheumatoid arthritis: facts and figures. *J Rheumatol* 1998;25 (Suppl. 53):8-12.

times the work disability rate of an age- and sex-matched population.<sup>27</sup> Lost earnings for RA patients have been estimated to be \$6.5 billion annually.<sup>28</sup>

**B. THE STANDARD OF CARE AND THE LIMITED TREATMENT OPTIONS AVAILABLE FOR RHEUMATOID ARTHRITIS**

**1. Early And Aggressive Treatment With DMARDs Is The Standard Of Care**

Because there is no known cure for rheumatoid arthritis, the ultimate goal in treating the disease is to induce a complete remission, which rarely occurs. More realistic goals of RA management are to control disease activity, alleviate pain, maintain physical function (especially to perform activities of daily living and work), maximize the patient's health related quality of life, and control or prevent joint damage. Because RA is a chronic progressive disease, proper management typically requires a lifelong coordinated effort involving medications, physical and occupational therapy, patient education, supportive services (when appropriate), and reconstructive surgery (when indicated). Periodic reassessment of disease activity, progression, and therapeutic efficacy, as well as vigilance to detect adverse effects, are essential and frequently require modification of the treatment regimen.<sup>29</sup>

RA treatment during the past 10 years has focused on early and aggressive use of DMARDs, which was primarily methotrexate until the past 4 years, when four new DMARDs and three new anti-inflammatory medications were approved. DMARDs interfere with the disease process and have the potential to modify the course of the disease. The ACR Guidelines recommend that DMARD therapy should be started within 3 months of diagnosis in the majority of patients with newly diagnosed RA. If repetitive flares occur, ongoing disease activity is present after 3 months of maximum therapy, or progressive joint damage is detected, then a switch to a different DMARD or addition of another DMARD is recommended.<sup>30</sup> Because not all patients have an adequate response to one DMARD alone, the use of combination DMARD therapy has come to play an important role in RA treatment.<sup>31</sup>

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27 Felts W et al. The economic impact of the rheumatic diseases in the United States. *J Rheumatol* 1989; 16:867-884.

28 See footnotes 26-27; ACR Guidelines Update 2002; Mitchell JM, et al. The importance of age, education, and comorbidity in the substantial earnings losses of individuals with symmetric polyarthritis. *Arthr Rheum* 1988;31(3):348-357.

29 ACR Guidelines Update 2002.

30 *Id.*

31 ACR Guidelines Update 2002; Kremer, JM. Rational use of new and existing disease-modifying agents in rheumatoid arthritis. *Annals of Internal Medicine* 2001;134(8):695-703; Arava® (leflunomide) Prescribing Information; Pincus T, et al. Combination therapy with multiple disease-modifying antirheumatic drugs in rheumatoid arthritis: a preventive strategy. *Annals Int Med* 1999; 131(10):768-774; Matteson

The DMARDs commonly used in RA treatment are Plaquenil (hydroxychloroquine), Azulfidine (sulfasalazine), methotrexate, Arava® (leflunomide), Enbrel® (etanercept), and Remicade® (infliximab).<sup>32</sup> In the United States, Plaquenil is often used as initial treatment in patients with early, mild disease.<sup>33</sup> Methotrexate is the most widely used DMARD; it is frequently added to Plaquenil and is the background DMARD for most DMARD combinations.<sup>34</sup> Remicade® is used in combination with methotrexate, after an inadequate response to methotrexate alone. Arava® and Enbrel® are used alone as alternatives to methotrexate or in combination with methotrexate after inadequate response to methotrexate alone.<sup>35</sup>

## 2. The Efficacy And Safety Limitations Of The Available DMARDs

HRG calls for the withdrawal of Arava® from the market given the availability of other therapies to treat RA. However, HRG does not objectively evaluate these alternatives relative to current medical knowledge and clinical practice. Some of the proposed alternatives are not viable for many patients. For example, HRG asserts that “rest and nutrition for acute attacks,” “exercise,” and “physiotherapy” are effective alternatives to Arava®. *See* Petition at 17. They are not alternatives to DMARDs, but provide only adjunct therapy. While exercise and rest are important additions to overall coordinated RA management and may help alleviate some symptoms, they are not the standard of care for treating active RA, because, above all, they do not prevent or slow progression of this disease. Surgery is also listed in the Petition as an alternative to Arava®. However, while surgery has a place as a reconstructive measure, it cannot be used to control disease activity. Even when indicated, it has its own attendant risks and is not an option for many arthritis patients due to their age, medical condition, or confounding factors associated with their disease.

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E, Anderson R. Rheumatoid Arthritis. In: Primer on the Rheumatic Diseases. Klippel JH, ed. edition 12, Arthritis Foundation, Atlanta, 2001. DMARDs are often given concomitantly with other drugs used for symptomatic relief, typically: (1) nonsteroidal anti-inflammatory drugs (NSAIDs), including the new selective cyclooxygenase-2 (COX-2) inhibitors, and (2) low-dose corticosteroids (glucocorticoids), such as prednisone, which are potent anti-inflammatory drugs. *Id.*

32 ACR Guidelines Update 2002. Although highlighted by HRG, older DMARDs, such as gold preparations, penicillamine, cyclosporine, azathioprine, and cyclophosphamide, have only very limited use in current practice, particularly in the United States. *See* ACR Guidelines Update 2002. Sulfasalazine is widely used in Europe, but less so in the United States. Although Plaquenil (hydroxychloroquine) is categorized as a DMARD, there is no objective evidence that it modifies the course of disease progression. Plaquenil is often used as initial therapy in patients with mild RA.

33 ACR Guidelines Update 2002; Matteson E, Anderson R. Rheumatoid Arthritis. In: Primer on the Rheumatic Diseases. Klippel JH, ed. edition 12, Arthritis Foundation, Atlanta, 2001.

34 ACR Guidelines Update 2002.

35 *Id.* Approximately 26 percent of Arava® use is in combination with methotrexate. Scott-Levin's Physician Drug and Diagnosis Audit, 2001.

HRG's analysis of alternative medications is incomplete and out of date. Although most of the other medications mentioned have an important place in the treatment of RA, it is grossly misleading for HRG to suggest that their safety and efficacy profiles are superior to Arava®. Each has a different mechanism of action than Arava®, not all are equally beneficial in any individual patient, and all have been associated<sup>36</sup> with serious and sometimes fatal adverse events, many of which were not identified in the clinical trials leading to approval of the respective drugs.

Likewise, many RA patients have pre-existing co-morbid conditions that contraindicate the use of certain prescription medications.<sup>37</sup> Moreover, it is typical of the disease that patients become refractory to a particular medication, or that efficacy decreases over time. Although monotherapy with methotrexate is usually effective for some period of time, it is common for patients to eventually "fail" this therapy and require addition or substitution of treatments – thus, the recent reports of combination therapy in RA.<sup>38</sup> This well-known phenomenon is a fundamental reason underscoring the still unmet need for more RA medications with differing mechanisms of action.

In addition, each of the medications listed by HRG as alternative therapies has been associated with rare but serious adverse events that can be life-threatening or fatal.

- Methotrexate is associated with sometimes fatal pulmonary events (interstitial pneumonitis),<sup>39</sup> hepatic events (including cirrhosis), hematologic events (including pancytopenia, agranulocytosis and aplastic anemia), serious infections (including opportunistic infections), hemorrhagic enteritis, reversible renal

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<sup>36</sup> As used in this Response, the term "associated" refers to a temporal relationship between the medications and the events, not necessarily to a determination of causation. Robinson WH et al: Review: Demyelinating and neurological events reported in association with TNF antagonism: *Arth Rheum* 2001; 44:1977-83; ACR Hotline: FDA Advisory Committee reviews safety of TNF inhibitors, ACR 9/24/01; Keane J et al: Tuberculosis associated with infliximab, a TNF $\alpha$  neutralizing agent *N Engl J Med.* 2001; 345: 1098-104; Mohan N et al: Demyelination occurring during anti TNF $\alpha$  therapy for inflammatory arthritides *Arth Rheum* 2001; 44: 2862-9; Shakoob N et al: Drug induced systemic lupus erythematosus associated with etanercept therapy. *Lancet* 2002; 359:579-80.

<sup>37</sup> E.g., the new biologic Remicade® (infliximab) has been contraindicated in patients with congestive heart failure due to observed further deterioration in these patients during Phase II clinical trials.

<sup>38</sup> Kremer, JM and Lee, JK, A long-term prospective study of the use of methotrexate in rheumatoid arthritis: Update after a mean of 53 months, *Arth and Rheum*, 1988; 31:577-584. O'Dell J, Haire C, Erikson N et al: Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three. *N Engl J Med.* 1996; 334: 1287-91. Tugwell P, Pincus T, Yocum D et al: Combination therapy with cyclosporin and methotrexate in severe RA. *N Engl J Med.* 1995; 333:137-141. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ et al: A trial of etanercept, a recombinant tumor necrosis factor receptor-Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med.* 1999; 340:253-9. Lipsky PE, van der Heijde, DM, St Clair EW, Furst, DE, Breedveld FC, Kalden JR, et al. Infliximab and Methotrexate in the Treatment of Rheumatoid Arthritis. *N Engl J Med.* 2000;343:1594-1602. Cohen S., Hurd E., Cush J., Schiff M., Weinblatt ME., Moreland LW. et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist (IL-1ra), in combination with methotrexate. *Arth Rheum* 2001; 46:614-24. Weinblatt ME, Kremer JM, Coblyn JS, Maier AM, Helfgott SM, Morrell M, Byrne VM, Kaymakjian MV, Strand V: Efficacy, Safety and Pharmacokinetics of the combination of methotrexate and leflunomide in patients with active rheumatoid arthritis. *Arth Rheum* 1999; 42:1322-8. Kremer JM, Genovese MC, Cannon GW et al: Concomitant leflunomide therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate: A randomized comparison of efficacy, safety, and tolerability compared to methotrexate alone. *Ann Int Med.* (accepted for publication).

<sup>39</sup> Zisman, DA, et al., Drug-induced pneumonitis: the role of methotrexate, *Sarc Vasc and Diff Lung Dis* 2001; 18(3): 243-252; Cannon GW Cerveny KC, Finck BK Enbrel ERA Investigators Group, Simpsn KM, Leflunomide Investigators Group, Strand V; Incidence and Risk Factors for Methotrexate-induced Pulmonary Disease during Treatment of Rheumatoid Arthritis. *Arthritis Rheum* 44: S341.

failure and severe skin reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis).<sup>40</sup>

- Azulfidine (sulfasalazine) is associated with sometimes fatal hematologic events (agranulocytosis and aplastic anemia), renal and hepatic damage, hypersensitivity reactions, irreversible neuromuscular and central nervous system changes, and fibrosing alveolitis. Severe skin hypersensitivity reactions have included Stevens-Johnson syndrome and toxic epidermal necrolysis. Hepatic events have included hepatitis, jaundice, cholestatic jaundice, fulminant hepatitis, hepatic necrosis, hepatic failure, and cirrhosis. Hemolytic anemia can occur in patients with underlying glucose-6-phosphate deficiency.<sup>41</sup>
- Enbrel® (etanercept) is associated with aplastic anemia, demyelinating neurologic diseases, tuberculosis, other opportunistic infections, and fatal cases of sepsis. Enbrel® is also associated with various opportunistic infections, including nasal and bronchial infections, *staphylococcus aureus* infection, and *E. coli* urinary tract infections.<sup>42</sup>
- Remicade® (infliximab) is associated with active tuberculosis, as well as other opportunistic infections, and deaths due to sepsis and tuberculosis.<sup>43</sup>
- Plaquenil® (hydroxychloroquine) is associated with rare irreversible retinal damage which can lead to visual loss. With overdose or with lower doses in hypersensitive patients, sudden respiratory and cardiac arrest has occurred. It is also associated with neuromuscular reactions, serious skin reactions such as Stevens-Johnson syndrome and exfoliative dermatitis, and hematologic events including aplastic anemia, granulocytosis, leukopenia, thrombocytopenia, and hemolysis in individuals with glucose-6-phosphate deficiency.<sup>44</sup>
- Injectable gold is associated with anaphylactic shock, hematologic events (aplastic anemia, hypoplastic anemia, agranulocytosis, pancytopenia, leukopenia, thrombocytopenia, hemorrhagic diathesis), hepatic events (cholestasis, toxic hepatitis, jaundice) interstitial pneumonitis or fibrosis, renal disease, and severe skin reactions such as exfoliative dermatitis.<sup>45</sup>
- Penicillamine is associated with sometimes fatal aplastic anemia, agranulocytosis, thrombocytopenia, Goodpasture's syndrome (a severe pulmonary-renal disease),

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40 Methotrexate prescribing information, revised August 28, 2001

42 Azulfidine® EN-tabs (sulfasalazine delayed-release tablets) prescribing information.

42 Enbrel® prescribing information; Ferraccioli G et al., Anticardiolipin antibodies in rheumatoid patients treated with etanercept or conventional combination therapy: direct and indirect evidence for a possible association with infections, *Annals of Rheumatic Disease*; 2002 61(4): 358-61; Mohan N et al: Demyelination occurring during anti TNF $\alpha$  therapy for inflammatory arthritides *Arth Rheum* 2001; 44: 2862-9. Shakoor N et al: Drug induces systemic lupus erythematosus associated with etanercept therapy. *Lancet* 2002; 359:579-80. Robinson WH et al: Review: Demyelinating and neurological events reported in association with TNF $\alpha$  antagonism: *Arth Rheum* 2001; 44:1977-83. ACR Hotline: FDA Advisory Committee reviews safety of TNF inhibitors, ACR 9/24/01. [www.fda.gov/medwatch/safety/1999/enbrel.html](http://www.fda.gov/medwatch/safety/1999/enbrel.html).

43 Remicade® prescribing information; Keane J, et al., Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent, *N Engl J Med.*; 2001 55 (15): 1098-104; ACR Hotline: FDA Advisory Committee reviews safety of TNF inhibitors, ACR 9/24/01. [www.fda.gov/medwatch/safety/2000/remicade.html](http://www.fda.gov/medwatch/safety/2000/remicade.html).

44 Plaquenil® (hydroxychloroquine) prescribing information.

45 Solganol® (aurothioglucose) prescribing information.

and myasthenia gravis. Serious events also include renal disease, toxic hepatitis, drug-induced lupus erythematosus, neuropathy, and severe skin reactions including pemphigus vulgaris, exfoliative dermatitis, and toxic epidermal necrolysis.<sup>46</sup>

- Imuran (azathioprine) is associated with severe leukopenia and thrombocytopenia, serious infections including opportunistic infections, malignancies, hypersensitivity reactions, hepatic events, and interstitial pneumonitis.<sup>47</sup>
- Neoral (cyclosporine) is associated with dose-related renal toxicity (including structural kidney damage) and with hepatic events. Hypertension is common. Higher doses used in organ transplantation may increase the susceptibility to infection and neoplasia. Cyclosporine has known interactions with many drugs such as various antibiotics, anti-fungals, anti-neoplastics, anti-inflammatory drugs such as NSAIDs and methylprednisolone, anti-convulsants, and histamine-2 receptor blockers.<sup>48</sup>
- NSAIDs, widely used in the symptomatic treatment of many acute and chronic inflammatory and painful conditions, are associated with sometimes fatal complications of peptic ulcer disease (especially gastrointestinal hemorrhage), fatal anaphylactoid reactions, and hepatic events including hepatic necrosis, jaundice, and fulminant hepatitis. In addition, NSAIDs are associated with renal damage, aseptic meningitis with fever and coma, hematologic events (including leukopenia, thrombocytopenia, aplastic anemia, agranulocytosis, and hemolytic anemia), and severe skin reactions such as Stevens-Johnson syndrome.<sup>49</sup>
- Glucocorticoids (“corticosteroids”, most often prednisone) are potent anti-inflammatory drugs used widely in the treatment of RA and other diseases. They are associated with many adverse events, especially with long-term use, even at the lower doses ( $\leq 10$  mg/day) usually used in RA, including increased susceptibility to and seriousness of infections (including opportunistic infections), cardiac ventricular wall rupture after recent myocardial infarction, and acute adrenal insufficiency in physiologic stress situations or with abrupt cessation of the glucocorticoid.<sup>50</sup> Other potentially serious adverse events include diabetes, hypertension, atherosclerosis, osteoporosis leading to fractures, a type of joint damage called avascular necrosis, glaucoma, and impaired wound healing.<sup>51</sup>

In short, use of every therapy currently indicated for the treatment of active RA has both recognized benefits and risks. Aventis does not refer to other RA medications for comparison

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<sup>46</sup> Cuprimine® (penicillamine) prescribing information.

<sup>47</sup> Imuran® (azathioprine) prescribing information.

<sup>48</sup> Neoral® (cyclosporine microemulsion) prescribing information.

<sup>49</sup> NSAID class labeling, e.g., Voltaren® (diclofenac) prescribing information; Tolman KG, Hepatotoxicity of Non-Narcotic Analgesics, *Am J of Med*; 1998 105: 13S-19S.

<sup>50</sup> Glucocorticoid class labeling, e.g. Deltasone® (prednisone) prescribing information.

purposes or to suggest that they are unsafe, but rather to offer perspective. These products, including Arava®, are indicated for treatment of a chronic disease with devastating complications, which can be life threatening. None of these therapies is risk free; however, the benefits of each outweigh their associated risks. Because RA is heterogeneous and affects each patient differently, each treatment must be individually selected for optimal use in each patient at their particular stage of the disease process. The balance of this Response will evaluate the efficacy and safety of use of Arava® and confirm its positive benefit-risk profile in the treatment of RA.

## II. ARAVA® IS A NOVEL THERAPY IN THE TREATMENT OF RHEUMATOID ARTHRITIS

Arava® is an isoxazole immunomodulatory agent with a unique mechanism of action. It inhibits *de novo* pyrimidine syntheses by reversibly blocking the enzyme dihydroorotate dehydrogenase (DHODH), resulting in antiproliferative effects on activated autoimmune lymphocytes important in the pathogenesis of RA.<sup>52</sup>

The NDA for Arava® was submitted to the FDA on March 10, 1998. Because Arava® was judged to offer a new therapeutic alternative in a debilitating, potentially life threatening disease, it was assigned priority review by the FDA in April 1998, and given a 1P designation, which is reserved for drugs that, if approved, would represent a significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a specific disease.<sup>53</sup> The FDA Arthritis Advisory Committee unanimously recommended approval on August 7, 1998,<sup>54</sup> and the NDA was approved on September 10, 1998. Arava® was the first DMARD indicated to retard structural damage as evidenced by x-ray erosions and joint space narrowing. Since 1998, Arava® has been used by over approximately 500,000 patients worldwide.

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51 ACR Ad Hoc Committee on Clinical Guidelines. Guidelines for monitoring drug therapy in Rheumatoid Arthritis. *Arthritis Rheum* 1996;39(5):723-731.

52 Fox RI, et al. Short analytical review: mechanism of action for leflunomide in rheumatoid arthritis. *Clin Immunol* 1999; 93(3):198-208; Fox RI. Mechanism of action of leflunomide in rheumatoid Arthritis. *J Rheumatol* 1998; 25 Supp 53:20-26; Kremer JM. Methotrexate and leflunomide: Biochemical basis for combination therapy in the treatment of rheumatoid arthritis. *Seminars in Arthritis and Rheumatism* 1999;29(1):14-26; Breedveld FC, et al. Leflunomide: mode of action in the treatment of rheumatoid arthritis. *Ann Rheum Dis* 2000; 59:841-849; Laan R, et al. Leflunomide and methotrexate. *Current Opinion in Rheumatology* 2001; 13: 159-163

53 See FDA/CDER Manual of Policies & Procedures, Priority Review Policy, MAPP 6020.3.

54 FDA Talk Paper, T98-54, September 11, 1998.

**A. THE PETITION MISREPRESENTS THE EFFICACY OF ARAVA® IN CLINICAL TRIALS**

A constant (but unsubstantiated) theme in the Petition is that Arava® is inferior to methotrexate and, at a minimum, is not equally effective compared with methotrexate. This claim is erroneous in both premise and fact. First, the length of time on any DMARD, including methotrexate, is ultimately limited by intolerance and/or loss of effectiveness.<sup>55</sup> Therefore, RA patients typically need to take many different DMARDs during the course of their disease.<sup>56</sup> It is, therefore, essential to have multiple alternatives for monotherapy, as well as options for various DMARD combinations.<sup>57</sup> Moreover, no recent DMARD approval (including Arava® and the biologic agents) for the treatment of active RA has been based on the demonstration of superior efficacy compared with methotrexate.

Second, as discussed below, the controlled clinical trial data demonstrate that, overall, Arava® and methotrexate have equivalent efficacy without consistent or meaningful clinical differences across studies. Third, the clinical trial data were extensively reviewed by the FDA and its Arthritis Advisory Committee prior to approval. HRG not only misrepresents the efficacy and safety data of Arava®, but it does not provide any new information to suggest that either the FDA or the Advisory Committee made a decision based on incomplete or incorrect information.

**B. CLINICAL TRIALS ESTABLISHED THE EFFICACY OF ARAVA®**

Arava® was studied in randomized, controlled clinical trials involving more than 2400 adult patients before it was first approved for use by a regulatory health authority. Three phase III controlled clinical trials (each of which was continued in blinded extension trials) established the efficacy of Arava® in reducing the signs and symptoms of RA, improving physical function, and retarding structural joint damage:

- **US301** was a randomized, double-blind, placebo-controlled study of 482 patients, with a primary endpoint at 12 months and continued double-blind treatment to 24 months. Leflunomide was compared with both placebo and methotrexate (plus folate). The ACR 20 Responder-at-Endpoint rates were statistically equivalent for leflunomide (41%) and

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<sup>55</sup> Wolfe F. The epidemiology of drug treatment failure in rheumatoid arthritis, *Baillier's Clinical Rheumatology* 1995; 9(4):619-632.  
<sup>56</sup> ACR Guidelines Update 2002.

<sup>57</sup> Contrary to the Petition, the value of any DMARD, including Arava®, in the treatment armamentarium is not based on demonstration of increased efficacy compared to methotrexate.

methotrexate (35%), and both were statistically significantly superior to placebo (19%).<sup>58</sup> Leflunomide and methotrexate were statistically significantly better than placebo by ACR 20 rates, including tender and swollen joint counts, global assessments, pain, ESR, CRP,<sup>59</sup> and physical function and health related quality of life assessments. Onset of action was faster with leflunomide, and leflunomide resulted in greater improvement in HAQ Disability Index, *see infra* subsection II.B.2., and equivalent slowing or inhibiting radiographically-assessed disease progression compared with methotrexate. The second year data showed maintenance of clinical and radiographic benefits at 24 months in both active treatment groups.<sup>60</sup>

- **MN301** was a randomized, double-blind, placebo-controlled, 6-month study of 358 patients, and the active comparator drug was sulfasalazine. The ACR 20 Responder-at-Endpoint rates were 49% for leflunomide, 45% for sulfasalazine, and 29% for placebo. Leflunomide and sulfasalazine were statistically equivalent and both were statistically significantly superior to placebo by ACR 20 rates and all components, HAQ Disability Index, and slowing or inhibiting radiographic disease progression.<sup>61</sup>
- **MN302** was a 999-patient randomized, double-blind study comparing leflunomide to methotrexate at 12 months. This study was not placebo-controlled, and concomitant folate administration was not required (only 10% of methotrexate patients received folate).<sup>62</sup> The ACR 20 Responder-at-Endpoint rate was 43% with leflunomide and 57% with methotrexate, which showed statistical non-equivalence; the differences in the components of the response criteria were small and not considered clinically meaningful. In addition, the two treatments were statistically equivalent for slowing or inhibiting disease progression by x-ray and in

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<sup>58</sup> This stringent primary analysis is described in more detail, *infra* at subsection II.B.1., but, in short, measures the percentage of patients that had an ACR 20 Response and completed the trial. Another analysis, the Last Observation Carried Forward ("LOCF"), measures the percent of patients that had an ACR 20 Response whenever they discontinued in the study, or at the end if they remained in the study to completion. The ACR 20 Response rates in the LOCF analysis in US301 were similar or leflunomide ( 52%) and methotrexate ( 46%), and both were superior to placebo ( 26%).

<sup>59</sup> ESR is erythrocyte sedimentation rate and CRP is C-reactive protein. Higher levels of either of these blood tests reflect degree of inflammation.

<sup>60</sup> Strand V, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Archives Int Med* 1999;159:2542-2550; Sharp JT, et al. Treatment with leflunomide shows radiographic progression of rheumatoid arthritis. *Arthritis Rheum* 2000;43:495-505; Cohen S, et al. Two-year, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. *Arthritis Rheum* 2001;44(9):1984-1992.

<sup>61</sup> Smolen JS, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double blind, randomized, multicentre trial. *Lancet* 1999;353:259-66; Arava® (leflunomide) prescribing information; Sharp JT, et al. Treatment with leflunomide shows radiographic progression of rheumatoid arthritis. *Arthritis Rheum* 2000;43:495-505. The ACR 20 Response rates in the LOCF analysis were 55% for leflunomide, 57% for sulfasalazine, and 29% for placebo.

<sup>62</sup> It is believed that folate decreases methotrexate toxicity, especially gastrointestinal symptoms and liver enzyme elevations (often called liver function tests or LFTs). ACR Ad Hoc Committee on clinical guidelines. Guidelines for monitoring drug therapy in Rheumatoid Arthritis. *Arthritis Rheum* 1996;39(5):723-731; Van Ede AE, et al. Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis. *Arthritis Rheum* 2001; 44(7): 1515-1524. Furst DE, Cohen S, Emery P et al: Does Folic Acid decrease the efficacy as well as the toxicity of methotrexate in RA. *Arth Rheum* 2001; 45:S373. Folate supplementation was mandated in US301, whereas only 10 percent of methotrexate patients in MN302 received folate supplementation.

an AUC analysis of ACR Response. *See infra* subsection II.B.1. Leflunomide had a more rapid onset of response.<sup>63</sup>

- **MN303** was a double-blind, 6-month extension of MN301. ACR 20 responses, x-ray benefit and improvements in physical function were maintained over 12 months in both leflunomide and sulfasalazine patients, and the two treatments were statistically equivalent in all clinical parameters studied.
- **MN305** was a double-blind extension of MNN301/303 for a second year. ACR 20 responses, x-ray benefits and improvements in physical function were maintained in year 2 in patients continuing leflunomide treatment. At month 24, leflunomide-treated patients had statistically significantly better ACR 20 Response rates, investigator and patient global assessments, HAQ Disability Index scores and x-ray benefit than sulfasalazine ; other efficacy parameters were similar in both treatment groups.<sup>64</sup>
- **MN304** was a double-blind extension of MN302 for a second year. ACR 20 responses, x-ray benefits and improvements in physical function were maintained in patients continuing a second year of leflunomide treatment. After 2 years of treatment, leflunomide and methotrexate had equivalent clinical efficacy by ACR Responses and HAQ Disability Index.<sup>65</sup>

These trials provide clear evidence of the important benefits provided by Arava®. Although this data were reported to the FDA in detail in the NDA and published in peer-reviewed journals, HRG failed to reference much of it – especially when the data were inconsistent with its position. The following discussion provides additional evidence of the proven efficacy of Arava®.

#### 1. Reduction In Signs And Symptoms

The FDA requires that clinical efficacy for the treatment of RA be measured using a defined composite index of multiple signs and symptoms, such as determining the proportion of patients who meet the American College of Rheumatology (“ACR”) criteria defining a clinical

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<sup>63</sup> Emery P, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology* 2000;39:655-665; Arava® (leflunomide) prescribing information; Sharp JT, et al. Treatment with leflunomide slows radiographic progression of rheumatoid arthritis. *Arthritis Rheum* 2000;43(3):495-505. The ACR 20 response rate (for LOCF) was 51% with leflunomide and 65% with methotrexate.

<sup>64</sup> Kalden JR, et al. Improved functional ability in patients with rheumatoid arthritis—long-term treatment with leflunomide versus sulfasalazine. *J Rheum* 2001;28(9): 1983-91; Scott DL, et al. Treatment of active rheumatoid arthritis with leflunomide: two year follow up a double blind, placebo controlled trial versus sulfasalazine. *Ann Rheum Dis*. 2001;60:913-923.

<sup>65</sup> Emery P, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology* 2000;39:655-665

response, known as an ACR 20 Responder.<sup>66</sup> An ACR 20 Responder must have at least 20 percent improvement demonstrated in 5 of 7 core set measures of disease activity, including both tender and swollen joint counts.<sup>67</sup> Using these criteria, Aventis applied a stringent primary analysis -- the ACR 20 Responder-at-Endpoint rate -- to the phase III clinical trial data.<sup>68</sup> In both placebo-controlled trials, Arava® monotherapy was statistically significantly superior to placebo in reducing the signs and symptoms of RA after 6 months in MN301 (ACR Responder-at-Endpoint: Arava®-49% vs. placebo-29%),<sup>69</sup> and after 12 months in US301 (41% vs. 19%), and statistically equivalent to the active comparator agents (methotrexate and sulfasalazine).<sup>70</sup>

HRG cites only the 12-month efficacy data from the MN302 study, where a difference in ACR 20 Responder-at-Endpoint rate was observed in favor of methotrexate (57%) over leflunomide (43%), although, as previously noted, the differences in the components were small and not meaningfully different from a clinical standpoint. However, HRG fails to reference the 12-month results of US301, in which there was no statistically significant difference in the ACR 20 Responder-at-Endpoint rate between Arava® (41%) and methotrexate (35%).<sup>71</sup> Indeed, the efficacy of Arava® was consistent across all trials, whereas the efficacy of methotrexate varied substantially between trials.<sup>72</sup> In addition to the efficacy demonstrated by ACR Response rates,

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66 FDA Guidance to Industry: Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis. *Clin* 1999 8:1-56; Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. *Arthritis Rheum.* 1993;36:729-740.

67 The core set measures used to determine whether a patient is a responder are tender and swollen joint counts, physician and patient assessments of disease activity, laboratory measures of disease activity (sedimentation rate or C-reactive protein), pain, and patient-reported assessment of physical function using a validated physical function instrument such as the Health Assessment Questionnaire. Felson DT, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995; 38(6): 727-735. An ACR 20 Responder may also meet criteria for higher thresholds of response; an ACR 50 or ACR 70 Responder is defined in a manner analogous to the ACR 20 Responder but with improvements of at least 50% or at least 70%, respectively.

68 The primary efficacy analysis for overall clinical response in the Arava trials was the ACR 20 Responder-at-Endpoint analysis, a stringent analysis in which an ACR 20 Responder-at-Endpoint is a patient who both (1) completed the study and (2) was an ACR 20 responder at the study endpoint. Additionally, dropouts for any cause were considered non-Responders, even if they had an ACR 20 Response at the time they left the study. Each trial was extended to a total of 2 years and demonstrated that the benefit at 1 year was maintained in year-2.

69 Smolen JS, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double blind, randomized, multicentre trial. *Lancet* 1999;353:259-66.

70 Strand V, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Archives Int Med* 1999;159:2542-2550. MN302 was not a placebo-controlled trial.

71 Arava® (leflunomide) prescribing information. There was also no statistically significant difference in ACR 20 Responder-at-Endpoint rate between leflunomide (49%) and sulfasalazine (45%) after 6 months in MN301. *Id.*

72 In the ACR 20 Responder-at-Endpoint analysis across all trials, 41-49% of the Arava®-treated patients completed the 6- or 12-month trial with at least a 20% response at the end of the trial. In the LOCF analysis, using the last study visit for patients who discontinued early, more than half of the Arava®-treated patients (51-55%) had at least a 20% response at their last study visit, one third (31-34%) had at least a 50% response, and 10-20% had at least a 70% response.

Unlike with Arava®, methotrexate efficacy varied considerably between trials. In US301 and MN302, rates ranged from 35% to 57% for the ACR 20 Responder-at-Endpoint rates, and in the LOCF analysis, ranged from 46% to 65% for ACR 20, 23% to 44% for ACR 50 and 9-16% for ACR 70 Responder rates. The reasons for this variability in methotrexate performance between US301 and MN302 are not clear, but it may have been influenced by differences in patient populations, absence of a placebo arm, and the fact that folate supplementation was used in only 10 percent of methotrexate of patients in MN302. Emery P, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology* 2000;39:655-665; Strand V, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Archives Int Med* 1999, 59:2542-2550. See also *supra*, fn. 62.

treatment with Arava® improved all of the individual components of disease activity consistently across the three trials.<sup>73</sup> It should be noted that the use of methotrexate with folate in US 301 most closely mirrors how that drug is prescribed and used in the United States.

Moreover, when the ACR 20 Response was analyzed over time, Arava® and methotrexate were not statistically different in either US301 or MN302. Whereas the ACR 20 analysis measures a response at one point in time, the Area Under the Curve (AUC) analysis measures the number of weeks a patient is an ACR 20 Responder, which provides important detail regarding the onset and time course of patient response. AUC analyses showed statistical equivalence between Arava® and methotrexate in US301 and MN302 and equivalence between Arava® and sulfasalazine in MN301.<sup>74</sup>

Analyses of response over time also demonstrated that the treatment effect of Arava® was rapid and sustained. Response was evident by 1 month, with further increases, which stabilized by 3-6 months and continued throughout the course of treatment.<sup>75</sup> In patients with pain and inflammation, the time to onset of effect is an important consideration. Initial response and sustained response occurred earlier with Arava® compared with methotrexate in both studies.<sup>76</sup>

## **2. Improvement In Physical Function**

Impairment in physical function may make it difficult to perform activities of daily living, resulting in work disability for many patients, and reducing health-related quality of life.<sup>77</sup> Maintaining physical function for activities of daily living and work, as well as health related quality of life, are important goals in RA management.<sup>78</sup>

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73 Arava® (leflunomide) prescribing information.

74 Strand V, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Archives Int Med* 1999;159:2542-2550; Arava NDA 20-905.

75 Arava® (leflunomide) prescribing information.

76 Strand V, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Archives Int Med* 1999;159:2542-2550; Emery P, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology* 2000;39:655-665. ACR 20 response was apparent at one month in 38% of patients treated with Arava compared to 24% with methotrexate in US301, 24% with Arava compared to 18% with methotrexate in MN302, and 31% with Arava compared to 19% with sulfasalazine in MN301. Arava® NDA 20-905.

77 Wolfe F, et al. The clinical value of the Stanford Health Assessment Questionnaire Functional Disability Index in patients with rheumatoid arthritis. *J Rheumatol* 1998;15(10):1480-1488; Strand V, et al. Function and health-related quality of life: results from a randomized controlled trial of leflunomide versus methotrexate or placebo in patients with active rheumatoid arthritis. Leflunomide Rheumatoid Arthritis Investigators Group. *Arthritis Rheum.* 1999;42(9):1870-8.

78 ACR Guidelines Update 2002.

Physical function was assessed by the HAQ Disability Index -- a recognized, validated instrument used to assess rheumatic disease-specific impairment.<sup>79</sup> The HAQ was completed by all patients in all phase III clinical studies. The ACR Response criteria were calculated using mean HAQ (MN301 and MN302) or modified HAQ (US301), as well as patient global assessment and patient assessment of pain. HRG dismisses the HAQ analysis, concluding without discussion that it measures primarily subjective endpoints, *see* Petition at 15, and disregarding patient perception entirely. In fact, impairment of physical function has predictive value for work and overall disability, cost, joint replacement surgery, and premature mortality.<sup>80</sup> In the clinical trials, treatment with Arava® resulted in statistically significant improvement compared with placebo in the HAQ Disability Index, as well as all 8 HAQ subscale scores in both phase III placebo-controlled trials.<sup>81</sup> In all trials, improvement in HAQ Disability Index subscales in the leflunomide treatment groups was clinically meaningful and, in most of the subscales, exceeded or approached twice the minimal clinically important difference established in the literature at 6, 12 and 24 months.<sup>82</sup> These data show that Arava® did not merely maintain

<sup>79</sup> The HAQ was developed to assess disease-specific physical function and degree of disability in patients suffering from RA. It consists of various questions relating to eight categories (dressing and grooming, rising, eating, walking, hygiene, reach, grip, and activities). Fries J, et al. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;23(2):137-145; Ramey DR et al. The Health Assessment Questionnaire 1995—Status and Review In: *Quality of Life and Pharmacoeconomics in Clinical Trials*, second edition, Spilker B, ed. Lippencott-Raven Publ, PA, c1996.

<sup>80</sup> Mitchell DM, et al. Survival, prognosis, and causes of death in rheumatoid arthritis. *Arthritis Rheum* 1986;29(6):706-714; Pincus T, et al. Prediction of long-term mortality in patients with rheumatoid arthritis according to simple questionnaire and joint count measures. *Ann Int Med* 1994;120(1):26-34; Wolfe F, et al. The long-term outcomes of rheumatoid arthritis. *Arthr Rheum* 1998; 41(6):1072-1082; Wolfe F, et al. Clinical and health status measures over time: prognosis and outcome assessment in rheumatoid arthritis. *J Rheumatol* 1991;18(9):1290-1297; Wolfe F. The prognosis of rheumatoid arthritis: assessment of disease activity and disease severity in the clinic. *Am J Med* 1997;103:12S-18S; Wolfe F, et al. The clinical value of the Stanford Health Assessment Questionnaire Functional Disability Index in patients with rheumatoid arthritis. *J Rheumatol* 1988;15(10):1480-1488; Fries JF, et al. Medical costs are strongly associated with disability levels in rheumatoid arthritis. *Arthritis Rheum* 1995;38(suppl.):S187; Singh G, et al. Long-term medical costs and outcomes are significantly associated with early changes in disability in rheumatoid arthritis. *Arthritis Rheum* 1996;39(suppl.):S318.

<sup>81</sup> Strand V, et al. Function and health-related quality of life: results from a randomized controlled trial of leflunomide versus methotrexate or placebo in patients with active rheumatoid arthritis. Leflunomide Rheumatoid Arthritis Investigators Group. *Arthritis Rheum*. 1999;42(9):1870-8; Tugwell P, et al. Clinical improvement as reflected in measures of function and health-related quality of life following treatment with leflunomide compared with methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 2000;43(3):506-514; Kalden JR, et al. Improved functional ability in patients with rheumatoid arthritis—long-term treatment with leflunomide versus sulfasalazine. *J Rheum* 2001;28(9): 1983-91.

<sup>82</sup> Wells G, et al. Important difference between patients with rheumatoid arthritis: the patient's perspective. *J Rheumatol* 1993;20:557-560. Kosinski M, Zhao SZ, Didhiya S, Osterhaus JT, Ware JE. Determining minimum clinically important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. *Arth Rheum* 2000;43:1478-87. Kujawski SC, Kosinski M, Martin R, Wanke LA, Buatti MC, Ware JE, et al. Determining meaningful improvement in SF-36 scale scores for treatment studies of early, active RA. *Arth Rheum* 2000; 43:S140. Samsa G, Edelman D, Rothman M, et al. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. *Pharmacoeconomics* 1999; 15:141-155. Tugwell P, Wells G, Strand V, Bombardier C, Maetzel A, Crawford B, Dorrier C, Thompson A: Clinical Improvement as Reflected in Measures of Function and health-related quality of life: Sensitivity and Relative Efficiency to Detect a Treatment Effect in a 12 month Placebo Controlled Trial Comparing Leflunomide with Methotrexate, *Arth Rheum* 2000; 43:506-14. Strand V, Cannon G, Cohen S, Ware J et al: Correlation of HAQ with SF-36: Comparison of Leflunomide to Methotrexate in patients with active RA. *Arth Rheum* 2001; 44:S187. Strand V, Bombardier C, Maetzel A, Scott D, Crawford B: Use of minimum clinically important differences [MCID] in evaluating patient responses to treatment of RA. *Arth Rheum* 2001; 44:S187. Zhao SZ, McMillen JI, Markenson JA, Dedhiya SD, Zhao WW, Osterhaus JT, Yu SS: Evaluation of the functional status aspects of health-related quality of life of patients with osteoarthritis. *Pharmacotherapy* 1999; 19:1269-1278. Ehrlich EW, Bolognese JA, Kong S, Watson DJ, Zeng K, Seidenberg BC: Improvements in SF-36 mental health domains with treatment of OA result of decreased pain and disability or independent mechanism? *Arth Rheum* 1998; 41:S221. Ehrlich EW, Davies GM, Watson DJ, Bolognese JA, Seidenberg BC, Bellamy N: Minimum perceptible clinical improvement with the WOMAC and global assessments in patients with osteoarthritis. *J Rheumatol* 2000; 27:2635-41. Angst F, Aeschlimann A, Stucki G: Smallest detectable and minimal clinically important differences of rehabilitation intervention with their

the physical function present at baseline, but actually improved it to a statistically and clinically meaningful degree.

In addition to the HAQ Disability Index, two other instruments were used in US301 to further evaluate physical function and health related quality of life, neither of which is mentioned by HRG. One method -- the Problem Elicitation Technique (PET) questionnaire -- is based on the patient identifying those physical activities that he or she considers most important (i.e., activities that are most affected by their disease and that they would most want to see improved).<sup>83</sup> In this analysis, patients treated with Arava® showed statistically significantly greater improvement compared with both placebo and methotrexate treatment groups.<sup>84</sup>

The second additional method used to evaluate improvement in physical function in US301 was the SF-36 -- a widely used instrument to assess generic health-related quality of life. This was the first randomized clinical trial to demonstrate reduction in all domains of health related quality of life in RA patients compared to the general population (age and gender matched).<sup>85</sup> Arava® treatment resulted in statistically significant improvements compared to placebo in the Physical Component Summary score and in 5 of the 8 SF-36 domains (physical functioning, body pain, general health perception, vitality, and social functioning). Arava® also was associated with statistically significant improvement in the Physical Component Summary score and in 2 SF-36 domain scores (body pain and vitality) compared with methotrexate.<sup>86</sup> As with the HAQ, the PET and SF-36 instruments are recognized as important instruments to assess

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implications for required sample sizes using WOMAC and SF-36 Quality of life measurement instruments in patients with osteoarthritis of the lower extremities. *Arth Care Res* 2001; 45:384-391. Wyrwich KW, Nienaber NA, Tierney WM, Wolinsky FD: Linking clinical relevance and statistical significance in evaluating intra-individual changes in HRQOL. *Medical Care* 1999; 37:469-78. Wyrwich KW, Tierney WM, Wolinsky FD: Further evidence supporting an SEM based criterion for identifying meaningful intra-individual changes in HRQOL. *J Clin Epidemiol* 1999; 52:861-73. Kosinski M, Zhao SZ, Didhiya S, Osterhaus JT, Ware JE. Determining minimum clinically important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. *Arth Rheum* 2000;43:1478-87.

83 Tugwell P, et al. Methotrexate in rheumatoid arthritis: Impact on quality of life assessed by traditional standard-item and individualized patient preference health status questionnaires. *Arch Intern Med* 1990; 150:59-62-62.

84 Strand V, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Archives Int Med* 1999;159:2542-2550; Strand V, et al. Function and health-related quality of life: results from a randomized controlled trial of leflunomide versus methotrexate or placebo in patients with active rheumatoid arthritis. Leflunomide Rheumatoid Arthritis Investigators Group. *Arthritis Rheum*. 1999;42(9):1870-8; Tugwell P, et al. Clinical improvement as reflected in measures of function and health-related quality of life following treatment with leflunomide compared with methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 2000;43(3):506-514.

85 Strand V, et al. Function and health-related quality of life: results from a randomized controlled trial of leflunomide versus methotrexate or placebo in patients with active rheumatoid arthritis. Leflunomide Rheumatoid Arthritis Investigators Group. *Arthritis Rheum*. 1999;42(9):1870-8. The SF-36 has proved to be valid and reliable in a large number of diseases in addition to RA (e.g., cardiovascular disease, low back pain, Type II diabetes, and osteoarthritis) Ware JE, et al. The MOS 36-item short form health survey (SF-36). *Medical Care* 1992;30(6):473-483; Ware JE, et al. *SF-36® Health Survey: Manual and Interpretation Guide*. Lincoln, RI: Quality Metric Incorporated, 1993, 2000; Ware JE and Kosinski M *SF-36 Physical & Mental Health Summary Scales: A Manual for Users of Version 1*, 2nd ed Lincoln, RI: Quality Metric, 2001.

86 Strand V, et al. Function and health-related quality of life: results from a randomized controlled trial of leflunomide versus methotrexate or placebo in patients with active rheumatoid arthritis. Leflunomide Rheumatoid Arthritis Investigators Group. *Arthritis Rheum*. 1999;42(9):1870-8; Tugwell P, et al. Clinical improvement as reflected in measures of function and health-related quality of life following treatment with leflunomide compared with methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 2000;43(3):506-514.

physical impairment and reductions in health related quality of life in RA patients. *See supra*, fns. 80 and 82.

### 3. Slowing Of Radiographic Progression

HRG also fails to note that Arava® significantly retarded or inhibited progression of RA as shown by radiographic evidence in both of the placebo-controlled trials.<sup>87</sup> This occurred at 12 months in US301 and at 6 months in MN301. In both trials, Arava® reduced the progression of structural joint damage by more than 75% compared to placebo.<sup>88</sup> In US301 and MN302, the slowing of progression was comparable for Arava® and methotrexate, with no consistent difference across the two studies.<sup>89</sup> These data are comparable to those reported for the other recently approved DMARDs.<sup>90</sup>

### 4. The Benefits Of Arava® Were Maintained In A Second Year Of Treatment

Double-blind treatment was continued to 24 months in the US301 trial and the extensions of the MN301 and MN302 trials. These 2-year data were published and available to HRG -- but ignored.<sup>91</sup> These data confirmed that clinical efficacy in Arava®-treated patients was sustained over 2 years of treatment. The benefits achieved during the first year of Arava® treatment -- reduction in signs and symptoms, improvements in physical function, and the slowing or inhibiting radiographic progression -- were maintained in patients continuing a second year of treatment.<sup>92</sup>

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87 As measured by total Sharp scores, which sum (add) erosions and joint space narrowing.

88 Of the placebo patients in US301, approximately 60% had received active treatment in an alternative therapy phase for a mean of 7 to 8 months after withdrawing from placebo treatment.

89 In the two trials comparing Arava® and methotrexate, the slowing of radiographic progression was statistically significant in favor of Arava® in US301 ( $p=0.0499$ ), and the two drugs were not statistically different in MN302, demonstrating overall similar effect. Of interest, US301 was also the first placebo-controlled trial to demonstrate the efficacy of methotrexate in slowing radiographic progression. Likewise, MN301 was the second placebo-controlled trial to demonstrate efficacy of sulfasalazine in slowing radiographic progression, and the slowing of progression with sulfasalazine was statistically equivalent to Arava® ( $p=0.3394$ ). Sharp JT, et al. Treatment with leflunomide slows radiographic progression of rheumatoid arthritis. *Arthritis Rheum* 2000;43(3):495-505.

90 Strand V, Sharp JT: Review: Radiographic Data from Recent randomized controlled trials in RA: What have we learned? *Arth Rheum* 2002; 46: (accepted for publication).

91 Cohen S, et al. Two-year, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. *Arthritis Rheum* 2001;44(9):1984-1992; Scott DL, et al. Treatment of active rheumatoid arthritis with leflunomide: two year follow up a double blind, placebo controlled trial versus sulfasalazine. *Ann Rheum Dis.* 2001;60:913-923; Kalden JR, et al. Improved functional ability in patients with rheumatoid arthritis—long-term treatment with leflunomide versus sulfasalazine. *J Rheum* 2001;28(9): 1983-91; Emery P, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology* 2000;39:655-665.

92 *Id.*

### III. THE PETITION MISREPRESENTS THE SAFETY OF ARAVA®

In addition to mischaracterizing the efficacy data, HRG posits a selective and misleading review of the clinical and post-marketing safety surveillance data. In fact, the clinical studies confirmed that Arava® is safe and effective when used according to the prescribing information, and nothing in the post-marketing experience contradicts that conclusion.

#### A. CLINICAL TRIALS ESTABLISHED THE SAFETY OF ARAVA®

The FDA's determination of Arava®'s safety was based upon an integrated clinical trial database containing safety data from over 2400 patients in phase II and III studies, including over 1300 rheumatoid arthritis patients receiving Arava®. This database also represents the largest blinded, controlled exposure for methotrexate therapy in RA.

#### EXPOSURE in Phase II and III Clinical Trials:

Treatment Group	Total Exposed	≥ 6 Months	≥12 Months	I year data Patient Years	2 year data Patient Years
LEF	1,339	1,011	838	2077	2467
MTX	680	549	497	936	1558
SSZ	133	76	23	258	244
PL	310	90	38	226	256

More than 800 Arava® patients were in the phase III studies alone. At the time the Arava® NDA was filed with the FDA, it was the largest database ever submitted for approval of a DMARD in RA. The 12-month primary safety analysis of the three phase III clinical trials was provided in detail in the Arava® NDA, and 2 year integrated safety data were thereafter provided to the FDA.<sup>93</sup>

Notwithstanding these substantial safety data, HRG refers to only limited results that appear to skew the safety analysis. For example, HRG suggests that “[in] assessing hepatotoxicity, the most weight . . . should be given to US301,” in which folate (which reduces not only side effects such as liver enzyme elevations, but may also reduce efficacy of

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<sup>93</sup> The phase III clinical trials, including the 2 year data from these trials, has been published. Strand V, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Archives Int Med* 1999; 159:2542-2550; Smolen JS, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double blind, randomized, multicentre trial. *Lancet* 1999;353:259-66; Cohen S, et al. Two-year, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. *Arthritis Rheum* 2001;44(9):1984-1992; Scott DL, et al. Treatment of active rheumatoid arthritis with leflunomide: two year follow up a double blind, placebo controlled trial versus sulfasalazine. *Ann Rheum Dis*. 2001;60:913-923; Kalden JR, et al. Improved functional ability in patients with rheumatoid arthritis—long-term treatment with leflunomide versus sulfasalazine. *J Rheum* 2001;28(9): 1983-91; Emery P, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology* 2000;39:655-665.

methotrexate) was required. *See* Petition at 3. HRG does not mention the results of MN302 (in which folate was not required and was taken by only 10 percent of methotrexate patients), where the incidence of adverse liver events with methotrexate was significantly higher than with Arava®, yet the incidence in Arava® treated patients in MN302 was comparable to US301. Later in the Petition, however, HRG reverses its position on the importance of US301 and disregards it, suggesting instead that MN302 establishes “superior” efficacy. *See* Petition at 16. An assessment of drug safety should not be based on selective and contradictory use of the same data.

As discussed below, not only was HRG selective in its use of data, but even the information cited does not support its position. The clinical trial safety data -- the very basis for the FDA’s approval of the Arava® NDA -- have not changed since they were submitted to the FDA. The data supported the FDA’s conclusion that Arava® could be safely used when it was first approved in 1998, and it still supports that conclusion.

**1. The Frequency And Severity Of Adverse Events Involving Arava® Were Similar To Those With Methotrexate And Sulfasalazine**

HRG selectively relies on data from one trial (US301) to suggest that patients treated with Arava® experienced adverse events of greater frequency and severity than those associated with the active comparator drugs. For example, HRG claims that more Arava® patients withdrew due to adverse events compared to methotrexate. In fact, the rate of withdrawal from US301 for serious adverse events was the same for Arava® and methotrexate, and the total number of treatment-related serious adverse events (as judged by the investigators, not the sponsor) was less with Arava®. The FDA mandated withdrawals for asymptomatic elevated LFTs. *See* Appendix B, Table 3. A clearer understanding of safety emerges from a review of the integrated adverse event data from all phase III clinical trials that were provided to FDA, as well as data from individual trials that were published but ignored by HRG:

- Serious adverse events<sup>94</sup> occurred in similar numbers of Arava® and methotrexate patients (and slightly less with sulfasalazine). Fewer Arava® patients had serious

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<sup>94</sup> The term “serious adverse events” is defined by the Code of Federal Regulations to include any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/ incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an

adverse events assessed by the investigator as treatment-related as compared to both methotrexate and sulfasalazine across all studies.<sup>95</sup> See Appendix B, Table 2.

- Serious adverse events considered by the investigator to be treatment-related and withdrawals due to treatment-related serious adverse events were less frequent with Arava® than with methotrexate plus folate in US301.<sup>96</sup>
- The treatment-related serious adverse events in the Arava® and placebo groups in US301 consisted of 1 patient in each group with asymptomatic LFT elevations not requiring hospitalization and 1 patient in each group with non-fatal sepsis. In contrast, the treatment-related serious adverse events in the methotrexate group consisted of 2 patients with asymptomatic LFT elevations not requiring hospitalization, 1 patient with pneumonia, 1 patient with interstitial pneumonitis, and 1 patient with fatal sepsis.<sup>97</sup>
- The year-2 incidence of serious adverse events for the year-2 cohort was similar across treatment groups (leflunomide = 25.3%; sulfasalazine = 26.7%; methotrexate = 20.8 in US301 and 27.2% in MN304).<sup>98</sup>
- Serious adverse events in year 2 assessed by the investigator as possibly treatment-related were similar among the Arava® and both methotrexate groups, and fewer than the sulfasalazine group.<sup>99</sup>
- In year-2, there were fewer withdrawals for all adverse events, including fewer withdrawals for serious adverse events and treatment-related serious adverse events in the Arava®-treated patients than in either of the methotrexate groups and fewer than in the sulfasalazine group.<sup>100</sup>
- Deaths occurred at a similar rate among the treatment groups in year 1 and year 2 of the phase III controlled trials. In the first year of the three phase III studies, death occurred

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emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. 21 CFR 314.80.

<sup>95</sup> See Appendix B, Table 2, which provides an overview of the Adverse Events (AEs) reported in the phase II (leflunomide patients only) and phase III clinical trials in the 1 year database of NDA 20-905.

<sup>96</sup> Strand V, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Archives Int Med* 1999;159:2542-2550. The authors state that serious adverse events assessed as treatment-related by the investigator were reported for 2 patients receiving Arava® (1.1%), 2 patients receiving placebo (1.7%), and 5 patients receiving methotrexate (2.7%). See also Appendix B, Table 3.

<sup>97</sup> *Id.*

<sup>98</sup> See Appendix B, Table 4. Of the patients in those studies who completed 12 months of treatment, 450 Arava®-treated patients entered a second year of double-blind treatment in US301, extension MN305, or extension MN304. In US301, 101 patients treated with methotrexate with folate continued for a second year. From MN302, 320 patients treated with methotrexate without folate entered the MN304 second year extension. From MN301/303, 60 sulfasalazine entered the MN 305 second-year extension. The patients who entered a second year of double-blind treatment were designated the "year-2 cohort" and were evaluated in a supplemental integrated analysis of safety in the second year of treatment. The 2-year safety analysis compared safety in the year-2 cohort second year of treatment to the first year of treatment in the same patients. In turn, year-1 of the year-2 cohort was compared to year 1 of the intent-to-treat (ITT) population (i.e., all patients randomized to receive at least one dose of study drug in phase III trials and extension). The leflunomide treatment groups from the three phase III trials were pooled for the supplemental 2-year safety analysis. Methotrexate treatment groups were not pooled because folate was required in US301 whereas only 10 percent of methotrexate patients in MN 302/304 received folate. The supplemental 2-year safety data analysis also included an additional 8 leflunomide patients and 8 methotrexate patients from 5 Canadian sites that were not a part of the primary 1 year data analysis because Canada joined the US301 study a year after the other sites.

<sup>99</sup> *Id.*

<sup>100</sup> *Id.*

in 0.7% of Arava®-treated patients which was similar to the rate in the sulfasalazine (0.8%), methotrexate without folate (1.2%), and methotrexate with folate (0.5%) groups.

- In year-2 of treatment, death occurred in 0.7% of Arava®-treated patients, which was less than in both of the methotrexate treatment groups (1.0% for methotrexate with folate in US301 and 2.2% for methotrexate without folate in MN302). No deaths occurred in the 60 sulfasalazine patients in year-2.
- Similar proportions of Arava® and methotrexate patients withdrew due to adverse events, and more withdrew on sulfasalazine, in the phase II and III NDA studies. *See* Appendix B, Table 2.
- Fewer adverse events assessed by the investigator as treatment-related, and less dose reduction due to adverse events, occurred in Arava®-treated patients than in the methotrexate or sulfasalazine patients in the phase II and III NDA studies. *Id.*

## **2. HRG Mischaracterized The Adverse Event Profile Of Arava® For Several Disease Endpoints**

HRG focuses on certain adverse events (while selectively ignoring others) that occurred during the clinical trials. For example, HRG mentions vasculitis and suggests that Aventis failed to report two clinical trial deaths associated with vasculitis.<sup>101</sup> This accusation is false and misleading. First, the eventual deaths of these two patients occurred long after they withdrew from the clinical trial, as is clear from the publication on which HRG relies. Second, both cases were reported to the FDA during the trial at the time the vasculitis was diagnosed, and both were detailed in the NDA submission. Third, both deaths were, in fact, reported by Aventis to the FDA after the trials were concluded.<sup>102</sup> Moreover, vasculitis is listed in the **Adverse Reactions: Cardiovascular** section of the prescribing information,<sup>103</sup> based on occurrence in the phase II and III clinical trials at a rate of 0.6% with Arava®, which was similar to methotrexate (0.6%) and to sulfasalazine (0.8%).<sup>104</sup>

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<sup>101</sup> HRG refers to a letter to the editor in 1999 describing two patients who withdrew from MN302 due to vasculitis and who subsequently died 10 months and more than 2 years later, respectively. *See* Petition, at p.13, citing Bruyn GAW, et al. Leflunomide for active rheumatoid arthritis. *Lancet* 1999; 353:1883.

<sup>102</sup> *Id.* Although neither of the eventual deaths occurred during the trial or the post-trial observation period, follow-up information was available at the time of the NDA submission (regarding the male patient who died 10 months after withdrawal from the trial) and was forwarded to the FDA in addition to being included in the NDA. The follow-up information regarding the other patient (a female who died more than 2 years after withdrawal from the trial) was reported to the FDA when the information became available through the publication to which HRG refers.

<sup>103</sup> Arava® prescribing information.

<sup>104</sup> Smolen JS, et al. Reply to Bruyn GAW et al. Leflunomide for active rheumatoid arthritis. *Lancet* 1999; 353: 1883-1884.

a. Hypertension

HRG is correct that hypertension was reported more often in Arava® patients than in the control groups, but HRG only tells half the story. Of the Arava® patients with hypertension, a significant proportion (ranging in the phase III clinical trials from 75% to 100%) had evidence of pre-existing hypertension, either from a diagnosis of hypertension at study entry or hypertensive blood pressure readings at baseline. The incidence of new-onset hypertension was low, and there was no significant difference among treatment groups.<sup>105</sup> Moreover, the potential causal impact of concomitant NSAID and steroid use could not be excluded, as all subjects with new onset hypertension were receiving one or both of those drugs.

b. Hepatic Events

Detailed analyses of liver enzyme elevations in the phase III studies of Arava® were provided in the NDA submission, including incidence and degree of elevation of both hepatic aminotransferases -- alanine aminotransferase (ALT) and aspartate aminotransferase (AST).<sup>106</sup>

HRG is correct that, in US301, mild elevations occurred more often in patients treated with Arava® (17.6%) than in patients treated with methotrexate with folate (11.0%).<sup>107</sup> However, HRG disregards the fact that the incidence of clinically significant elevations (>2xULN)<sup>108</sup> and the subset of marked elevations (>3xULN) in Arava®-treated patients was similar to the methotrexate with folate group in US301 and much less than the methotrexate without folate group in MN302.<sup>109</sup> These clinically significant elevations -- both moderate (>2 to ≤ 3xULN) and marked (> 3xULN) -- in Arava® patients were generally reversible while continuing treatment or with dose reduction or discontinuation.<sup>110</sup>

HRG also focuses on two patients in the phase III clinical trials who had ALT elevations of 39xULN and 80xULN respectively, but fails to note that both cases were detailed in the NDA submission and the etiologies for both were confounded by other factors, as assessed by the

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<sup>105</sup> These ranged from 0 to 2.2% in the Arava® groups, 0 to 1.1% in the placebo groups, 0.4 to 1.6% in the methotrexate groups, and 0.8% in the sulfasalazine group.

<sup>106</sup> Because ALT is more sensitive to elevation than AST, and because patients in the studies with AST elevation also had ALT elevation (generally to a higher level), ALT elevations are shown in the appendix. ALT elevations are categorized based on the highest elevation for an individual patient. See Appendix B, Table 5.

<sup>107</sup> Mild ALT elevations (>1.2 to ≤2x ULN) occurred in 14.4% to 17.6% of Arava®-treated patients across the phase III trials, see *id.*, Table 5, and 98 percent of these normalized to < 1.2xULN generally while continuing treatment.

<sup>108</sup> ULN = Upper Limits of Normal.

<sup>109</sup> See Appendix B, Table 6; Arava® prescribing information.

<sup>110</sup> See Appendix B, Table 6. For all clinically significant elevations (>2x ULN), there was no difference in normalization rate with Arava (49/59, 83%) and methotrexate (148/174, 85%). Additionally, when all ALT elevations (> 1.2x ULN) are considered, the normalization

FDA.<sup>111</sup> It is important to note that in the NDA, 14 other cases of severe (>8xULN) ALT elevations did not involve Arava®: 1 in a placebo-treated patient, 2 in sulfasalazine-treated patients, and 11 in methotrexate-treated patients.

In short, the phase III clinical trials showed that the incidence of clinically significant liver enzyme elevations in Arava®-treated patients was similar to the incidence in patients on methotrexate with folate and lower than in patients on methotrexate without folate. Most ALT elevations were mild, and elevations were generally asymptomatic and reversible. Furthermore, the incidence of these events during the second year of Arava® treatment was not higher than during the first year of treatment, indicating that incidence does not increase with extended duration of treatment.<sup>112</sup> Accordingly, there is no basis for concluding that the clinical trials evidence any greater risk of hepatotoxicity, as defined by elevated LFTs, in Arava® patients compared to methotrexate patients.

c. Lymphoma

HRG suggests without basis that Arava® is associated with an increased risk of lymphoma. However, in the clinical trial data in the Arava® NDA submission, the overall incidence of malignancies did not substantially differ between treatment groups, including placebo. Various malignancies were reported in all groups, but frequencies were low and there was no clustering of findings in particular organs. Furthermore, the 2-year data for the active treatment groups did not demonstrate a higher incidence of malignancy for Arava®.

Rheumatoid arthritis is believed to be associated with an increased risk of lymphoproliferative disorders. In the absence of any clinical trial evidence of increased incidence of malignancy in Arava® patients, but based on the known increased risk of lymphoproliferative disorders associated with the use of some immunosuppressive medications, the **Warnings** section in the prescribing information clearly states:

Malignancy

The risk of malignancy, particularly lymphoproliferative disorders, is increased with the use of some immunosuppression medications. There is a potential for

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rate was higher in Arava-treated patients than in methotrexate-treated patients: 173/186 (93%) for Arava compared to 243/278 (87%) for methotrexate.

<sup>111</sup> Both patients were taking other drugs associated with hepatic events (one was taking sustained release niacin and lovastatin and the other was taking diclofenac with pre-existing Hepatitis C infection and had recently tapered her own prednisone dose, without knowledge of her treating physician. Both patients discontinued leflunomide treatment, with cholestyramine washout; and liver enzyme elevations resolved once the other drugs associated with potential hepatic toxicity were discontinued.

<sup>112</sup> In year-2, both ALT elevations and abnormal LFTs reported as adverse events occurred with lower frequency compared to year-1 as shown in Appendix B, Table 7. Two patients had ALT elevations >3x ULN that had not reversed to <2x ULN at the end of the study, but they subsequently reversed on follow-up.

immunosuppression with ARAVA. No apparent increase in the incidence of malignancies and lymphoproliferative disorders was reported in the clinical trials of ARAVA, but larger and longer-term studies would be needed to determine whether there is an increased risk of malignancy or lymphoproliferative disorders with ARAVA.

**d. Other Serious Adverse Events Of Interest With DMARD Therapies**

The controlled phase III trials provided no evidence that other adverse events of a serious nature that are considered related to DMARD therapies occurred more frequently with Arava® than with methotrexate or sulfasalazine treatment. There were no cases of interstitial pneumonitis, renal failure, or agranulocytosis in the Arava®-treated patients (representing 1333 patient years of exposure over 2 years of treatment in the phase III studies and 2467 patient years in the combined phase II and III clinical trials over two years), although these events were seen in the methotrexate and sulfasalazine control groups in the same phase III clinical trials over the same time period with less drug exposure (i.e., fewer patients exposed and fewer patient years of exposure).<sup>113</sup>

**3. The Year-2 Clinical Trial Safety Data Are Consistent With the Year-1 Data**

The adverse event profile of Arava® during the second year of treatment was similar to that during the first year of treatment, with no new types of adverse events emerging. The incidence of liver enzyme elevations decreased in the second year of treatment. Long-term information on the safety of therapy over 2 years supports its continued tolerability without emergence of new patterns of adverse events, either serious or non-serious, and with a diminished overall adverse event rate in a second year of treatment.

Based on the clinical data, there is no basis for concluding that methotrexate or sulfasalazine are “safer” than Arava®. To the contrary, analysis of the safety data from the controlled phase III studies shows that the overall percentage of patients with treatment-related serious adverse events and withdrawals due to serious adverse events (treatment related or not) was generally similar with Arava®, methotrexate, and sulfasalazine administration.

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<sup>113</sup> For example, there were two cases of agranulocytosis in the sulfasalazine patient group. Sulfasalazine also had the highest incidence of lymphoproliferative disorders. In the methotrexate-treated patients, there was renal failure, as well as four cases of interstitial pneumonitis (one of which was fatal) and one case of interstitial fibrosis. The rate of nonfatal sepsis was higher in the methotrexate groups than in the Arava® group. No Arava® patients developed pancytopenia, whereas pancytopenia in a methotrexate patient led to fatal pneumonia. The incidence of vasculitis was similar among the treatment groups in the clinical trials, and all were less than 1 per 100 patient years; rheumatoid vasculitis is a known extra-articular manifestation of RA.

## **B. HRG MISCHARACTERIZES THE POST-MARKETING ADVERSE EVENT PROFILE OF ARAVA®**

As with all other treatments for RA -- and most other prescription drug products -- adverse events have been reported in association with the post-marketing use of Arava®. Rather than reviewing those reports objectively in the context of the disease state and its associated morbidities, background incidence of certain events, polypharmacy (multiple medications) and the presence or lack of confounding factors, HRG offers yet another selective and inaccurate interpretation of the data.<sup>114</sup> As discussed below, an objective review of the post-marketing data confirms that there is no factual basis to conclude that the risk profile for Arava® is less favorable than that of other available DMARD therapies. This Response will address the various categories of adverse events mentioned by HRG in the Petition.

### **1. Limitations Of Post-Marketing Data**

In evaluating post-marketing data, it is important to understand the limitations of “spontaneous” reports and the purpose of reviewing such data. Spontaneously reported post-marketing information is evaluated with regard to potential new adverse health consequences and/or an increased incidence or severity of known risks.<sup>115</sup> The number of cases reported may vary considerably depending on the treatment; comparisons with other agents or estimated background rates of events in a given disease are difficult. However, the likelihood of under-reporting is lower with a newer drug such as Arava® than with other established, widely used therapies, such as methotrexate. Under-reporting is more likely with an older drug, such as methotrexate (used for 25 years and formally approved for RA in 1986).<sup>116</sup> Other factors that may affect the reporting of adverse events include: novelty of the event; severity of the event; perceived relationship to drug administration; adverse effects reported with similar drugs; physician awareness; previous reports of an adverse reaction (either in clinical trials or post-marketing surveillance data); and media interest.<sup>117</sup>

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<sup>114</sup> The search that HRG conducted using the FDA's AERs database was not exhaustive and did not capture all events reported for either Arava® or methotrexate. For most disease endpoints identified in the Petition, more adverse events were reported for methotrexate than for Arava®.

<sup>115</sup> PhRMA/FDA/AASLD Drug-Induced Hepatotoxicity White Paper – Postmarketing Considerations, November 2000 (the “White Paper”), p.3.

<sup>116</sup> Tsong Y, Comparing reporting rates of adverse events between drugs with adjustment for year of marketing and secular trends in total reporting, *J of Biopharm Stat*, 1995; 5(1): 95-114

<sup>117</sup> White Paper, p.3.

Another recognized limitation of spontaneous reporting is that many events have no more than a temporal association with the use of a drug, and differential reporting can make the benefit-risk profile of two drugs appear very different when, in fact, they are not.<sup>118</sup> As noted in a recent PhRMA/FDA/AASLD White Paper, “[w]ith the exception of some drug-specific diseases or symptoms . . . , the risk in unexposed patients (background risk) is never zero, so that reports of a drug association may be incorrect, and instead reflecting only background occurrence of the event.”<sup>119</sup> As stated in the FDA’s MedWatch form, anecdotal case reports do not establish causation – this is particularly the case in a disease with well recognized co-morbidities

The following discussion addresses HRG’s distorted review of the post-marketing data.

## 2. Post-Marketing Reports Of Hepatic Events.

Analysis of spontaneously reported hepatic events requires objective consideration of several factors, none of which appear to have been addressed by HRG. First, concomitant use of Arava® with other treatments for RA, including DMARDs, in addition to other confounding factors, make determination of a causal relationship between Arava® and any given event uncertain. For example, methotrexate, sulfasalazine, gold, azathioprine and cyclosporine have all been associated with hepatic events. Second, because RA is a systemic disease that can affect many extra-articular organs, underlying disease activity must also be considered as a potential causal factor, in addition to frequent co-morbid conditions such as cardiovascular disease. Third, hepatic events have been reported with other drugs, including both prescription and non-prescription drugs used in the treatment of RA. When complete information is lacking, as is often the case with post-marketing surveillance data, it is difficult to determine whether any or all of these potential contributing factors may be responsible for the adverse events reported following Arava® use.

Aventis has applied standardized case definitions and criteria for assessing causation with respect to all serious and non-serious reports of hepatic events from post-marketing clinical trials and post marketing surveillance.

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<sup>118</sup> *Id.* (Emphasis added).

<sup>119</sup> *Id.*

a. September 1998 to September 2001

During the 3-year period from September 1998 to September 2001, Aventis received 126 reports of adverse hepatic events (including serious and non-serious) that were classified as possibly associated with Arava® use, utilizing criteria for definition, classification, and analytical methods described by an international panel of experts for drug-induced hepatotoxicity.<sup>120</sup> The majority of these cases were classified as hepatocellular, with some cholestatic or mixed pattern events.

Of all hepatic adverse event reports, 23 were associated with a fatal outcome where *any* hepatic event was reported; a fatal hepatic event was specifically reported in 11 of the 23 cases. In the remaining 12 of these 23 cases, liver abnormalities were only one of several events in patients with multiple morbidities, and were not reported to be the cause of the fatal outcome.

In order to better understand these fatal events, Aventis consulted an outside expert, Professor Dominique Larrey, of the Hepatology and Transplant Unit, School of Medicine, Montpellier, France, to review the 23 cases in detail. Dr. Larrey concluded that none of the cases exhibited a definite causal relationship to Arava® administration; and that Arava® possibly could have had a contributory role in six of the reported cases due to the temporal relationship between Arava® use and the event. He considered the data to be consistent with a rare potential for hepatotoxicity, based primarily on the increases in ALT and the number of hepatic events reported.<sup>121</sup>

It is generally recognized that accurate incidence rates for adverse events cannot be established from spontaneous post-marketing surveillance data due to the absence of a certain and defined denominator (the total number of patients who were prescribed the treatment and complied with the prescription), as well as the variable degree of reporting adverse events, influenced to some degree by the perceived or documented safety profile of the agent at the time of its approval; specific adverse event labeling, and the well recognized degree of under-reporting inherent in a spontaneous reporting system. Furthermore, the nature of a voluntary reporting system often results in collection of incomplete information, and subsequent follow-up reports may be confused and counted as new events. Nonetheless, reporting rates may be roughly

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<sup>120</sup> Benichou C, Danan G. Causality assessment of Adverse Reactions to Drugs-I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *Journal Clinical Epidemiology* 1993;46:1323-1330.

<sup>121</sup> The 1/21/02 Expert Report of Professor Dominique Larrey has previously been provided to the FDA.

estimated using as a denominator the number of patient years of exposure calculated from product sales information.

Based on the available data, an estimated overall reporting rate for fatal hepatic events (11 cases) is 5.7/100,000 patient years. As noted, after application of internationally recognized case definitions and causality criteria, as well as analysis by an external expert hepatologist, a possible association was assessed in 6 of the 11 fatal hepatic cases.<sup>122</sup> The estimated reporting rate for these 6 possible fatal hepatic reactions is 2.25/100,000 patient years. As a point of reference, the occurrence rate of fatal hepatic events in the general population has been estimated by EMEA to be 11.7/100,000 patient years.<sup>123</sup>

b. **September 2001 to March 2002**

During the 6 month period from September 2001 through March 2002, Aventis received 24 reports of adverse hepatic events that were classified as possibly associated with Arava® administration, using the definitions, classifications, and analytical methods identified above. Distribution according to the type of liver injury reflects the same profile as in the previous three-year period, with a predominant hepatocellular pattern. In addition to these 24 cases, there were three cases where a hepatic event (liver failure) was reported as the fatal event. Of these three cases, however, none was assessed as possibly related to Arava® therapy: in one case, autopsy revealed hepatitis B infection; the second case was confounded by multiple concomitant medications; and the third case lacked any clinical information for assessment.<sup>124</sup>

Since first marketed, the prescribing information for Arava® has contained information about potential hepatotoxicity in the **Warnings** section, including monitoring recommendations. The rare serious hepatic events observed in the post-marketing period do not alter the positive benefit-risk profile of Arava®.<sup>125</sup>

3. **Post-Marketing Reports Of Lymphoma**

Aventis has received 13 spontaneous reports of lymphoma from 1998 to March 2002. In 5 of the 13 cases, the reporting physician assessed the event as unrelated to Arava® therapy. In

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<sup>122</sup> *Id.*

<sup>123</sup> EMEA Benefit-Risk Assessment for Arava® (available to FDA upon request). Exposure data represents the three years from September 1998 through September 2001. If all 23 cases were considered to be causally related, the occurrence rate would be 11.9/100,000 patient years.

<sup>124</sup> These cases have not yet been reviewed by Dr. Larrey.

<sup>125</sup> As previously noted, Aventis is working with the FDA to update the prescribing information to include additional data regarding the rare serious post-marketing hepatic events reported in association with Arava®.

those cases where sufficient information was available (11 out of 13 cases), excluding one case of interrupted therapy, symptoms that led to the diagnosis of lymphoma occurred between 2 and 6 months after the first Arava® dose. Occurrence of malignancy after such short-term exposure is considered an unlikely case for drug-induced pathology.<sup>126</sup> Most patients had received concomitant or previous long-standing treatment with other DMARDs, including methotrexate; persistent active RA and prolonged use of immunomodulatory treatments, such as DMARDs, are associated with a greater risk for lymphoma in patients with RA.<sup>127</sup> In addition, methotrexate has been associated with lymphomas that occurred during treatment and regressed upon discontinuation of this therapy.<sup>128</sup> The post-marketing reports in patients taking Arava® have not demonstrated such a pattern.

In the general population in 1997, the age-adjusted incidence rate of lymphoma was 15.8 per 100,000. The 1993-1997 age-adjusted incidence rate was 16.0 per 100,000. An increased incidence of lymphoma and/or lymphoproliferative disorders is believed to be associated with the underlying inflammatory RA disease process.<sup>129</sup>

Assuming as a worst case analysis -- that all 13 reported cases were causally associated with Arava® -- the observed reporting rate in Arava®-treated patients would be approximately 4.9 cases of lymphoma per 100,000 patient years -- lower than the estimated incidence rate of lymphoma in the general population. Post-marketing case reports of lymphoma therefore do not suggest evidence of a new safety signal,<sup>130</sup> as previously stated, the prescribing information includes a warning regarding this potential risk. *See supra*, Section III.A.2.c.

#### **4. Post-Marketing Reports Of Hematologic Events.**

It is difficult to interpret many reports of hematologic events because of: (i) hematologic abnormalities associated with RA; (ii) use of other medicines associated with hematologic adverse events; and (iii) pre-existing conditions in some patients. For example, methotrexate and sulfasalazine are associated with severe and sometimes fatal hematologic events. Nevertheless, on February 23, 2000, the **Warnings, Precautions, and Adverse Reactions** sections of the

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<sup>126</sup> *Cancer Principles and Practice of Oncology*, 6<sup>th</sup> ed, 2001.

<sup>127</sup> *Id.*; ACR Hotline: FDA Advisory Committee reviews safety of TNF inhibitors, ACR 9/24/01. *See also* Appendix C, List of 70 additional lymphoma/RA references.

<sup>128</sup> Genovese M. Musculoskeletal Syndromes in Malignancy. In: Kelley's Textbook of Rheumatology, 6th edition, Ruddy S et al, eds., WB Saunders Co, Phila 2001; Weinblatt M. Methotrexate. In: Kelley's Textbook of Rheumatology, 6th edition, Ruddy S et al, eds., WB Saunders Co, Phila 2001.

<sup>129</sup> Ries CAF, Eisner MP, Kosary CL, et al. SEER Cancer Statistics Review, 1993-1997, National Cancer Institute. NIH Pb. No. 00-2789. Bethesda, MD 2000.

Arava® prescribing information were amended (following FDA approval) to inform physicians that there had been rare spontaneous reports of pancytopenia in patients receiving Arava®. The prescribing information also included the following statement:

In most cases, patients received concomitant treatment with methotrexate or other immunosuppressive agents, or they had recently discontinued these therapies; in some cases, patients had a prior history of a significant hematologic abnormality. If ARAVA is used in such patients, it should be administered with caution and with frequent clinical and hematologic monitoring.

Aventis communicated these labeling changes to health care providers in a Dear Doctor letter dated March 21, 2000, which indicated the need to monitor for hematologic effects when used in combination with other hematotoxic DMARDs, which also require hematologic monitoring.

In the **Warnings** section of the prescribing information, hematologic monitoring is recommended for patients at increased risk of hematologic toxicity. In the **Adverse Reactions** section of the approved prescribing information, thrombocytopenia, leukopenia, and anemia are listed. On February 23, 2000, this section was amended (following FDA approval) to include post-marketing events of pancytopenia. Moreover, the **Warnings** section was also amended at that time to state that Arava® is not recommended in patients with severe immunodeficiency, bone marrow dysplasia or severe uncontrolled infections.<sup>131</sup>

Accordingly, the post-marketing data do not provide evidence of a greater risk of hematologic events than what is already referenced in the prescribing information.

##### 5. Post-Marketing Reports Of Dermatologic Events

On February 23, 2000, following receipt by Aventis of reports of Stevens-Johnson syndrome (“SJS”) and toxic epidermal necrolysis (“TEN”), the **Warnings** and **Adverse Reactions** sections of the prescribing information were amended (following FDA approval) to include SJS and TEN as well as erythema multiforme to inform physicians of the occurrence of these rare events and to provide recommendations for the drug elimination procedure. Aventis communicated these changes in labeling to health care providers in a Dear Doctor letter dated March 21, 2000.

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<sup>130</sup> Use of the term “signal” does not mean that a finding of causation between the drug and the event(s) has been established; rather, the term refers to surveillance information that suggests a need to conduct additional evaluation and/or analysis.

<sup>131</sup> Aventis has also been working with the FDA to update the hematologic monitoring recommendations contained in the prescribing information.

The number of reports for these events has remained stable since launch, despite increased exposure to Arava®. In many of these reported cases, confounding factors, including concomitant medications such as antibiotics and NSAIDs, which are also associated with these severe skin reactions, were present.

Neither the Petition nor the post-marketing surveillance data provide evidence of significantly greater risk of severe dermatologic events with Arava® than with other DMARDs. The reports remain rare and are adequately described in the prescribing information.

#### **6. Post-Marketing Reports Of Hypertension**

HRG claims that physicians are uninformed about the risk of hypertension because the prescribing information does not mention hypertension as a post-marketing adverse event. This argument is specious. Table 5 in the prescribing information identifies adverse events occurring in 3 percent or greater of clinical trial patients; hypertension is specifically mentioned under the heading “Cardiovascular.”

#### **7. Post-Marketing Reports Of Pregnancy**

HRG does not claim that post-marketing data require withdrawal of Arava®. Instead, HRG briefly discusses the pre-clinical toxicology data, but makes no specific recommendation. These data, as well as half-life of the active metabolite and elimination process to remove any effect of active drug were extensively discussed at the FDA Arthritis Advisory Committee hearing. The resulting recommendations are reflected in the label and include a washout procedure using 8 g of cholestyramine 3 times per day for 11 days (representing conservative estimates regarding blood levels and half life of the active metabolite), as well as two blood level determinations indicating no active drug (or metabolite) prior to pregnancy (offered by the sponsor upon request without cost to the patient).<sup>132</sup>

HRG also notes reports of post-marketing experience of maternal exposure to Arava®, concluding that “safe” levels of maternal exposure are unknown. This topic was covered in great detail in the FDA Arthritis Advisory Committee hearing, and, further, the boxed warning at the

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<sup>132</sup> The effectiveness of the cholestyramine washout procedure was tested in phase I trials, in addition to the one study referenced by HRG. HRG also distorts the safety profile of Arava® in its discussion of half-life and elimination. First, the Petition mistakenly suggests that a long half-life makes Arava® inherently unsafe. This is simply wrong. There are drugs with very short half-lives that can be unsafe and drugs with long half-lives that are safe. Second, the Petition suggests that since Arava has a long half-life, it may be stored somewhere in the body and have negative effects a long time after discontinuation. This is again false. There is no pharmacokinetic evidence for storage or compartmentalization of Arava or its metabolites anywhere in the body. Instead, Arava's long half-life is due to enterohepatic recycling in the liver, which sends the active metabolite from the liver to the bile and from the bile to the GI tract, where it is reabsorbed into the body. In turn,

beginning of the Arava® prescribing information expressly states that “Pregnancy must be excluded before the start of treatment . . . Arava® is contraindicated in pregnant women, or women of childbearing potential who are not using reliable contraception. . . . Pregnancy must be avoided during Arava® treatment . . . .”<sup>133</sup>

Aventis nevertheless continues to evaluate the clinical impact of exposure during pregnancy and is sponsoring a multi-center cohort study established by the Organization of Teratology Information Services (OTIS). The program provides counseling as well as post-marketing surveillance relative to the potential teratogenicity of Arava®. The study will document pregnancy outcome with respect to the presence or absence of a pattern of malformation in liveborn infants in women with first-trimester prenatal exposure to Arava®. Secondary endpoints to be evaluated include the rate of spontaneous abortions or stillbirth, pre- or post-natal growth deficiency, and premature delivery.<sup>134</sup>

#### **8. Post-Marketing Reports Of Gastrointestinal Events**

HRG does not suggest that Arava® should be withdrawn due to post-marketing reports of severe diarrhea. Instead, HRG notes that more reports were identified for Arava® than for methotrexate. Based on data from the controlled clinical trials, it is not surprising that more post-marketing reports of GI events were received with respect to Arava® treatment, because the incidence in these clinical studies was higher in patients receiving Arava® compared with those receiving metrotrexate.

Neither the character nor frequency of post-marketing surveillance adverse events indicate a greater risk of gastrointestinal events with Arava treatment than was observed in the clinical trials, and described in detail in the product label.

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cholestyramine enhances elimination of Arava® by interrupting (and preventing) the enterohepatic recycling process in the GI tract, where the active metabolite binds with the cholestyramine, thus preventing reabsorption into the body.

<sup>133</sup> HRG’s allegation that evidence of minimal maternal exposure proves that the warning is ineffective is equally specious. Under this theory, no product with any warnings of serious adverse events before or during pregnancy should be marketed. Moreover, HRG offers no evidence suggesting that the physicians in the reported cases were unaware of the warning.

<sup>134</sup> HRG questions the effectiveness of the wash-out procedure to remove or reduce plasma levels of the active metabolite. The drug elimination procedure in the prescribing information is designed to achieve nondetectable plasma levels of <0.2 mg/L (0.02 µg/ml). This level is more than 136 and 123 times lower, respectively, than C<sub>max</sub> levels in rats and rabbits, which did not cause embryotoxicity or teratogenicity. Dr. Robert Brent, a leading teratologist and FDA consultant, notes in a recent article (that HRG cites but ignores on this point, see Petition at 14) that a 100-fold reduction represents a conservative approach. Brent, RL Teratogen Update: Reproductive Risks of Leflunomide (Arava); A pyrimidine Synthesis Inhibitor: Counseling Women Taking Leflunomide Before or During Pregnancy and Men Taking Leflunomide Who are Contemplating Fathering a Child, *Teratology* 2001; 63: 106-112. Finally, it should be noted that post-washout M1 (active metabolite) plasma levels were not detected in 97 percent of the post-marketing reports of washout. This is convincing evidence of the effectiveness of the cholestyramine washout procedure.

## 9. Post-Marketing Reports Of Weight Loss

HRG refers to weight loss as an adverse event reported more frequently in Arava® than methotrexate treated patients. Not only is it difficult to relate weight loss in individual patients with administration of Arava® (or other DMARDs), but a unified mechanism to explain these observations is lacking. Based on limited observations in the phase II trials with Arava® treatment, the phase III randomized controlled trials specifically included physical and laboratory evaluations when clinically significant weight loss was observed. Across all phase III trials, few reports of treatment-associated weight loss required these pre-specified, additional analyses. Mean changes in weight, lipid profiles and other parameters, including serum total protein and albumin levels, in the leflunomide groups compared with placebo or active comparators failed to identify treatment associated changes.

Although it is difficult to evaluate post marketing surveillance reports of treatment-associated weight loss, it is likely that multiple etiologies explain these observations. Although patients with poorly controlled, active RA frequently complain of fatigue and malaise associated with elevated IL-6 levels, increased production of pro-inflammatory cytokines including TNF $\alpha$  and IL-1 in active rheumatoid arthritis result in profound systemic manifestations of malaise and fatigue, characterized as an anorectic/catabolic state. Weight loss may therefore result from organic (gastrointestinal disorders, connective tissue disease, endocrine, infection, malignancy, pulmonary, and neurologic), psychological and/or idiopathic etiologies. To determine whether reported weight loss is due to the underlying inflammation of rheumatoid arthritis or its treatment may not only be difficult but, in fact, impossible.<sup>135</sup> Anecdotal reports of weight loss as well as weight gain, and positive as well as negative changes in lipid profiles have occurred with other recently approved biologic and synthetic DMARDs.<sup>136</sup> To date, it has not been possible to ascertain whether these changes are treatment related or clinically meaningful.

When other gastrointestinal symptoms, including anorexia, nausea, vomiting, and diarrhea are reported, weight loss may reflect treatment associated adverse events. With Arava treatment, reports of weight loss have not included either baseline bodyweights or the period of time when weight loss was observed/reported. Nor were relevant clinical data provided, making it virtually impossible to establish a treatment associated causal relationship.

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<sup>135</sup> Cope AP: Regulation of autoimmunity by proinflammatory cytokines. *Curr Opin Immunol* 1998; 10:669-76.

Of the five case reports cited by HRG,<sup>137</sup> one patient discontinued Arava® and initiated etanercept therapy, and reportedly weight remained stable after discontinuation of Arava®. The four other patients continued on Arava® treatment due to good clinical responses, and their weight stabilized after the initial self-limited reports of weight loss. Based on the above analysis, the post-marketing reports do not reflect any new signal or an increased frequency or severity of weight loss. Accordingly, the information in the prescribing information adequately warns of a potential for weight loss in association with the use of Arava®.

\* \* \* \* \*

For the reasons stated above, post-marketing surveillance data do not represent a reliable comparison between a recently approved treatment such as Arava® and the standard of care, methotrexate, used for the past 25-30 years and specifically approved for the treatment of RA in 1986. It is important to remember that concern regarding LFT elevations with methotrexate therapy remain; specific guidelines for monitoring treatment have facilitated broad utilization in RA without requiring liver biopsies prior to treatment initiation and at intervals thereafter.<sup>138</sup> Familiarity with methotrexate therapy without requiring pre- and interim-treatment liver biopsies, has evolved over 16-25 years of clinical use, indicating that rheumatologists will carefully monitor DMARD therapies for active RA, recognizing they offer significant clinical benefits, but are nonetheless associated with significant potential risks. These treatments require detailed knowledge of the underlying autoimmune disease and careful monitoring of its therapy.

As a conservative estimate, RA patients have at least 30-40 years of active disease, and will need more treatments than are currently available to remain physically active and able to engage in work and social activities they deem important. Arava, as well as other recently approved DMARDs, represents a significant addition to the therapeutic armamentarium. However, even if a patient had the best and most prolonged clinical response to each of these therapies (as predicted by the clinical trials), used in a conservative, sequential fashion, they will not be sufficient in treating this lifelong debilitating disease with its associated co-morbidities.

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136 Vis M, Nurmohamed MT, Wolbink G et al: Short term effects of infliximab on lipid profiles in patients with RA *Ann Rheum Dis* 2002; 61:S75.

137 Coblyn JS, et al. Leflunomide - Associated weight loss in rheumatoid arthritis. *Arthritis Rheum* 2001; 44(5):1048-1051.

138 Kremer JM, et al. Methotrexate for rheumatoid arthritis: suggested guidelines for monitoring liver toxicity. *Arthritis Rheum* 1994;37(3):316-328; ACR Ad Hoc Committee on clinical guidelines. Guidelines for monitoring drug therapy in Rheumatoid Arthritis. *Arthritis Rheum* 1996;39(5):723-731.

Despite the approval of 7 new treatments for RA (4 new DMARDs and 3 COX-2 inhibitors) in the last 4 years, this disease still represents a significant unmet clinical need.

#### **IV. THE BENEFITS OF ARAVA® OUTWEIGH ASSOCIATED RISKS**

A substantive benefit-risk analysis for a RA treatment must be based on a clear understanding of the underlying disease and available therapies, as well as a thorough evaluation of safety and efficacy data. Rather than offering a reasoned, scientific evaluation, HRG cites clinical and post-marketing data without providing appropriate context. This unbalanced and selective approach does a disservice to the many thousands of patients who benefit from Arava® therapy.

Rheumatoid arthritis is a serious, crippling disease, with a high personal and socio-economic cost. There is no known cure. The risks and benefits of Arava® must be evaluated in the context of the manifestations and severity of the disease, and the strengths and limitations of other available therapies. All DMARDs have efficacy in the treatment of RA -- and all are associated with serious adverse events and require careful clinical and laboratory monitoring. A wide choice of DMARDs is needed in clinical practice to address issues of tolerability and decreased efficacy over time, especially in a disease that may last for 20 to 30 years, or more. Arava® has a unique mechanism of action that prevents the production of T-cells through the inhibition of pyrimidine synthesis -- targeting the disease process of RA. As demonstrated herein, a comprehensive analysis of the data compels the conclusion that the benefits of Arava® therapy outweigh known risks.

These conclusions are reinforced by two recent studies. One, a placebo-controlled study, confirms significant efficacy of Arava® when used in combination with methotrexate. The second, a 40,000 patient retrospective cohort study, shows that Arava®-treated patients generally had fewer adverse events overall than patients taking methotrexate or other DMARDs.

##### **A. THE PLACEBO-CONTROLLED STUDY OF COMBINATION ARAVA® AND METHOTREXATE SUPPORTS THE POSITIVE BENEFIT-RISK PROFILE FOR ARAVA®**

Arava® and methotrexate have different mechanisms of action -- inhibition of pyrimidine synthesis (Arava®) versus inhibition of intracellular purine pathways of metabolism resulting in modulation of cytokine and adenosine levels (methotrexate) -- which suggests a potential for

benefit in combination through complementary actions, especially in patients with inadequate response to monotherapy with either drug.

US4001 was a phase IIIb (post-marketing) study of combination Arava® and methotrexate.<sup>139</sup> The study evaluated the efficacy and safety of adding Arava® in RA patients inadequately responding (with active disease) to methotrexate, as compared to adding placebo to methotrexate.<sup>140</sup> It was a 6-month, multi-center trial involving 263 patients that was placebo-controlled, randomized, and double-blind. At the end of the 6-month study, patients were allowed to enter an open label extension phase for an additional 6 months. Patients on placebo were switched to Arava® at that time without using a loading dose. During the open-label phase, patients remained blinded to their original randomized treatment arm.<sup>141</sup>

### 1. Efficacy Results

US4001 demonstrated the efficacy of adding Arava® in RA patients who had active disease while on methotrexate alone.<sup>142</sup> The ACR20 Responder-at-Endpoint rate after adding Arava® (46%) was more than twice that after adding placebo (20%). When Arava® was added to ongoing methotrexate therapy, more than half of these patients (52%) were ACR 20 Responders at their last study visit compared to 23% receiving placebo. One-half of the Arava®-treated patients who were ACR 20 responders were also ACR 50 responders (at least 50% improvement). The ACR 50 and ACR 70 (at least 50% and 70% improvement, respectively) responder rates for Arava® were statistically significantly higher than placebo rates. The substantial benefit was also observed with regard to physical function. HAQ Disability Index improved significantly with the addition of Arava® compared to the addition of placebo. US4001 has provided additional support for the efficacy of Arava® compared to

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<sup>139</sup> Kremer JM, et al. Concomitant leflunomide therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate: A randomized comparison of efficacy, safety, and tolerability compared to methotrexate alone. *Annals Int Med* 2002 (accepted for publication); Kremer JM, et al. The combination of leflunomide and methotrexate in patients with active rheumatoid arthritis who are failing on MTX treatment alone: a double-blind placebo controlled study. *Arthritis Rheum* 2000; 43(9):S224; Furst DE, et al. Adding leflunomide to patients with active rheumatoid arthritis while receiving methotrexate improves physical function and health-related quality of life. *Arthritis Rheum* 2000; 43(9): S224.

<sup>140</sup> It should be noted that study 4001 was not a comparison of Arava plus methotrexate combination therapy versus methotrexate monotherapy; rather, it was a comparison of Arava versus placebo when added to background MTX in patients with persistent active disease while on methotrexate alone. These were patients who were selected for tolerating MTX monotherapy without LFT elevation. Therefore, the patients randomized to adding placebo would be expected to have a low incidence of LFT elevations, which was in fact the case.

<sup>141</sup> Kremer JM, et al. Concomitant leflunomide therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate: A randomized comparison of efficacy, safety, and tolerability compared to methotrexate alone. *Annals Int Med* 2002 (accepted for publication); Kremer JM, et al. The combination of leflunomide and methotrexate in patients with active rheumatoid arthritis who are failing on MTX treatment alone: a double-blind placebo controlled study. *Arthritis Rheum* 2000; 43(9):S224; Furst DE, et al. Adding leflunomide to patients with active rheumatoid arthritis while receiving methotrexate improves physical function and health-related quality of life. *Arthritis Rheum* 2000; 43(9): S224.

<sup>142</sup> *Id.*

placebo, in this case when added to background methotrexate treatment, demonstrating that patients who are inadequately responding to methotrexate can achieve clinically and statistically meaningful improvement by adding Arava®.

## 2. Safety Results

The safety findings of this phase IIIb combination therapy study -- the type and frequency of adverse events -- were consistent with those reported in clinical trials evaluating Arava® monotherapy. No clinical hepatic adverse events (i.e., a clinical diagnosis, as opposed to laboratory abnormalities alone) were reported during the 6-month, placebo-controlled study or the subsequent 6-month, open-label extension. Analysis of laboratory values showed that most of the ALT and AST elevations were mild ( $\leq 2 \times$  ULN), as they were in the phase III monotherapy studies. The incidence of clinically significant ( $>2 \times$  ULN) ALT elevation and the subset of marked ALT elevations ( $>3 \times$  ULN) after adding Arava® to ongoing methotrexate was within the range observed with Arava® monotherapy in the phase III trials. The highest ALT elevation was  $4.8 \times$ ULN.<sup>143</sup>

HRG assumes, based solely on a study report of one patient with liver cirrhosis confounded by many years of methotrexate treatment (which is associated with cirrhosis), that "the temptation to combine leflunomide and methotrexate holds many dangers." See Petition at 6. US4001 demonstrated that adding a lower initial dose of Arava® than is recommended for monotherapy,<sup>144</sup> with subsequent increase or decrease as appropriate for the individual, allowed the combination to be used effectively with a safety profile consistent with that seen in the phase III monotherapy studies of Arava®. Aventis currently is in discussion with the FDA regarding the addition of information relating to this study to the prescribing information.<sup>145</sup>

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<sup>143</sup> See Appendix B, Table 8.

<sup>144</sup> A lower dose than recommended for Arava monotherapy was used. The loading dose 100 mg daily for 2 days, rather than 3 days, and the initial maintenance dose was 10 mg daily, rather than 20 mg, which was adjusted upward or downward as necessary.

<sup>145</sup> Additionally, Aventis has recently completed Study HWA/486/4002. This multinational study was designed to evaluate whether the combination of leflunomide and sulfasalazine was superior to sulfasalazine alone, for the treatment of active RA, in patients who were non-responders after 24 weeks of leflunomide. Dosing levels contained in the U.S. prescribing information for monotherapy were used for a 6 month open label period, at the conclusion of which non-responders to leflunomide monotherapy were randomized to either sulfasalazine or placebo. Of the 968 patients initially treated with leflunomide, only 106 patients were non-responders who advanced to the second phase of the trial, which was such a small sample size that no meaningful comparisons could be drawn. In short, there was a substantially higher than expected response to leflunomide monotherapy (672 patients).

## B. THE COHORT STUDY

The relative safety of Arava® is further supported by the results of a retrospective cohort study of more than 40,000 RA patients.<sup>146</sup> Aventis used the claims database of a large managed care organization and compared the rates of liver, blood, skin, hypertension, and other adverse events among users of Arava®, alone and in combination with other DMARDs, to rates among users of methotrexate and other DMARDs, alone and in combination. The cohort of patients mirrored the larger RA population within the United States in terms of age, sex, and drug treatment. It is the largest cohort study of DMARD therapies in RA patients involving head-to-head comparisons of DMARDs.<sup>147</sup>

The results show that Arava® monotherapy is associated with fewer adverse events overall (12.20 AEs per 100 patient years) than other DMARDs, including methotrexate (18.85). Arava® monotherapy is also associated with a statistically significantly lower incidence of hypertension and respiratory events than other DMARD monotherapies, including methotrexate. The incidence of adverse events for other outcomes (hepatic, hematologic events, skin disorders, and pancreatitis) were not statistically different (though the rates were lower) than the other DMARDs.<sup>148</sup> Moreover, the combination of Arava® and methotrexate had significantly lower overall incidence of adverse events than the two comparator combinations (leflunomide plus other DMARDs and methotrexate plus other DMARDs). Finally, the mortality rate among Arava® users was lower than the comparison groups (there was one death in the Arava® group, 9 in the methotrexate group, and 82 in the DMARD group); these rates, however, were not statistically different. These results are shown in the following table, and the rates shown are reported per 100 patient years (except for mortality, where the rates are per 100,000 persons). This table also captures the total patient years for each DMARD or DMARD combination.

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<sup>146</sup> Cannon GW, Holden WL, Hochberg M, Juhaeri J, Dai W, Scarazzini L, Stang P. Adverse Events with Disease Modifying Antirheumatic Drugs: a Cohort Study With Comparison of Leflunomide with other DMARDs. (submitted for publication). In addition to the Cohort study, Aventis performed five additional epidemiologic analyses of the available data, which were provided to the EMEA/CPMP and to the FDA, all of which confirm the positive benefit-risk profile for Arava®.

<sup>147</sup> The cohort study design allowed for the determination of person-time exposure of individuals, i.e., the time (in years) that a person is at risk for the development of a particular adverse event (the denominator), and whether that person actually had the event (if yes, the numerator). The resulting incidence rate -- the numerator divided by the denominator -- can be further adjusted for the potential confounding effects of age, sex, and other medical conditions, which may distort the true association between drug use and adverse event.

<sup>148</sup> Arava® monotherapy had a higher, though not significantly different, incidence of hematologic events than methotrexate (0.14 per 100 PY vs. 0.08 per 100 PY).

	LEF (2 166 PY)	MTX (4808 PY)	Other DMARD (15717 PY)	NSAID (7028 PY)	COX-2 (3894 PY)	LEF + MTX 1024 PY)	LEF + other DMARD (2719 PY)	Other DMARD + MTX (8621 PY)
Any AE	12.20	18.85	18.89	40.37	33.78	5.31	7.40	8.55
Hepatic	0.45	0.70	0.58	1.35	1.07	0.53	0.24	0.34
Hematologic*	0.14	0.08	0.24	0.20	0.13	n/c	0.04	0.10
Skin*	n/c	0.12	0.10	0.02	n/c	n/c	0.04	0.03
Hypertension	3.98	6.65	6.10	16.77	14.18	1.68	2.47	2.75
Pancreatitis*	0.24	0.25	0.33	0.53	0.10	0.14	0.18	0.16
Respiratory	2.40	5.26	4.84	9.21	7.69	1.71	1.62	2.31
Mortality**	121.9	279.6	469.5	92.0	n/a	145.2	201.5	156.2

\*For hemotologic, skin, and pancreatitis, there were too few events or too little person-time for the mathematical model to adjust for age, sex, and comorbidities in all exposure groups

\*\*Rates per 100,000 persons

As noted above, the data for the Cohort Study came from a managed care organization claims database. Limitations of such a database include lack of indicators of disease severity, limited clinical detail, little or no data on compliance and use of over-the-counter drugs, as well as patient history. Nevertheless, the data are consistent with the conclusion that Arava® has a safety profile similar to the other DMARDs, including methotrexate. To be sure, HRG has offered no valid analysis to the contrary.

## V. THE STANDARD FOR WITHDRAWAL CANNOT BE MET

Arava® (leflunomide) Tablets is a “new drug” as defined under section 201(p) of the Federal Food, Drug & Cosmetic Act (“FFDCA”), 21 USC 321, and it is the subject of an approved NDA, 21 USC 355. Following approval of a NDA, the Secretary is authorized to withdraw approval of a new drug only under limited circumstances (pursuant to the section 505(e) of the FFDCA) and only after giving due notice and an opportunity for hearing to the applicant. In order to withdraw an application, the Secretary must determine that at least one of the following facts is present:

1. clinical or other experience, tests, or other scientific data show that a drug is unsafe for use under the conditions of use that formed the basis for approval of the application;
2. new evidence of clinical experience evaluated together with the evidence available when the application was approved, shows that the drug is not shown to be safe for use under the conditions of use that formed the basis for approval of the application; or
3. new information evaluated together with the evidence available when the drug was approved, shows that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling.<sup>149</sup>

Moreover, HRG has requested the Secretary to “immediately remove” Arava® from the market. The only authority to do so is “if the Secretary finds that there is an imminent hazard to the public health, he may suspend the approval” of a NDA immediately.<sup>150</sup> This extraordinary action may be undertaken “only in the exceptional case of an emergency, which does not permit the Secretary to correct it by other means.”<sup>151</sup>

As demonstrated above, HRG has failed to prove any of the bases for withdrawal:

1. Arava® is not “unsafe” and has a safety profile comparable to other available DMARDs;
2. There is no new evidence of clinical experience warranting withdrawal; and
3. There is no new information that suggests that Arava® does not have the effect it purports to have.

Indeed, the overwhelming weight of the data -- including the most recent clinical and other information -- provides further evidence of the positive benefit-risk profile of Arava®. The Petition, therefore, is unsupported and must be denied.

## **VI. CONCLUSION**

The benefit-risk profile of Arava® remains positive, and nothing HRG has submitted demonstrates otherwise. RA is a severe, chronic and disabling disease with no known cure. The arsenal of therapies available to treat RA is limited, and all of them have certain drawbacks. Unfortunately, there is no panacea for treating RA, and no single DMARD is effective for all

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<sup>149</sup> 21 USC 355(e).

<sup>150</sup> *Id.* This authority cannot be delegated.

<sup>151</sup> Sen. Rep. No. 1744 at 7, 87<sup>th</sup> Cong., 2d Sess. (1962).

patients throughout the course of their disease. Arava® is an important option available to physicians who treat patients with RA, as reflected in the unsolicited letter submitted by Dr. Gary S. Firestein, M.D., Chair of the Arthritis Advisory Committee, in opposition to the Petition. *See* Appendix A.

The randomized, controlled, phase III clinical trials demonstrate that Arava® is both safe and effective when used in accordance with the FDA approved prescribing information, and nothing in the post-marketing experience suggests otherwise. Thus, the legal standard applicable to the withdrawal of an NDA has not been met by HRG, and the Petition should be denied.

**SUBMITTED BY:**

**AVENTIS PHARMACEUTICALS INC.**  
August 8, 2002

**Aventis Pharmaceuticals**



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August 8, 2002

**NEW CORRESPONDENCE**  
*NC*

Lee Simon, M.D.  
Director  
Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Building CRP2, Mail Stop HFD-550  
9201 Corporate Blvd.  
Rockville, MD 20850

**NDA 20-905**  
**Arava® (leflunomide) Tablets**

**Response to FDA Request for Information**

Dear Dr. Simon:

Reference is made to a telephone conversation on August 7, 2002 with Ms. Jane Dean in regard to filing under the Arava NDA 20-905 the Aventis response to the Citizen's Petition that was dated March 28, 2002.

We are enclosing with this letter copies of the Aventis response to the Citizen's Petition.

If you have any questions or comments in regard to this communication, please do not hesitate to contact me at 908-231-3907.

Sincerely,

  
Jerry Kliniek  
Regulatory Liaison

Attachments: Desk Copy: Dr. Lee Simon and additional copy to be filed under NDA 20-905

**ORIGINAL**





DIVISION OF RHEUMATOLOGY, ALLERGY AND IMMUNOLOGY  
SCHOOL OF MEDICINE  
9500 Gilman Drive  
La Jolla, Ca 92093-0656

GARY S. FIRESTEIN, M.D.  
*Professor of Medicine and Chief*

Tel: (858) 534-2359  
Fax: (858) 534-2606

June 10, 2002

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 increasingly 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 morbid condition; and 2) aggressive treatment can alter the natural history of the disease.

With regard to some of the specific toxicity issues raised in the document, one can stipulate that leflunomide can be hepatotoxic. However, the information provided in the petition does not accurately

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 Merck 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,

Gary S. Firestein, M.D.  
Professor of Medicine  
UCSD School of Medicine

Chairman  
FDA Arthritis Advisory Committee



## APPENDIX B

### CLINICAL TRIAL EFFICACY AND SAFETY TABLES

Efficacy results from the Phase III clinical trials and the US 4001 study of combination Arava plus methotrexate are provided in Table 1 showing ACR response rates, HAQ Disability Index which measures physical function, and total Sharp scores which measure x-ray progression.

Study# Design	Pts at BL	Treatment Group (n)	ACR≥20% Responder-at- Endpoint <sup>3</sup> (% of pts)	ACR Responder <sup>2</sup> rates (LOCF)			HAQ Disability Index <sup>4</sup>		Sharp score (xray) <sup>5</sup>	
				ACR≥20% (% of pts)	ACR≥50% (% of pts)	ACR≥70% (% of pts)	Mean BL	Mean change	Mean BL	Mean change
US 301 12 mo PC, R, DB	482	LEF (182)	41 <sup>a</sup>	52 <sup>a</sup>	34 <sup>af</sup>	20 <sup>ae</sup>	1.30	-0.45 <sup>ae</sup>	23.11	0.53 <sup>ad</sup>
		PLA (118)	19	26	8	4	1.31	0.03	25.37	2.16
		MTX (180)	35 <sup>a</sup>	46 <sup>a</sup>	23 <sup>a</sup>	9	1.30	-0.26 <sup>d</sup>	22.76	0.89 <sup>c</sup>
MN 301 <sup>6</sup> 6 mo PC, R, DB	358	LEF (130)	49 <sup>b</sup>	55 <sup>a</sup>	33 <sup>b</sup>	10 <sup>c</sup>	1.65	-0.56 <sup>ag</sup>	46.26	1.23 <sup>a</sup>
		PLA (92)	29	29	14	2	1.59	-0.08	46.18	5.88
		SSZ (132)	45 <sup>c</sup>	57 <sup>a</sup>	30 <sup>b</sup>	8	1.50	-0.37 <sup>d</sup>	41.86	2.32 <sup>d</sup>
MN 302 12 mo R, DB	999	LEF (501)	43	51	31	10	1.50	-0.44	24.94	2.48
		MTX (498)	57 <sup>e</sup>	65 <sup>e</sup>	44 <sup>e</sup>	16 <sup>e</sup>	1.52	-0.54 <sup>g</sup>	24.60	1.62
US 4001 6 mo PC, R, DB	263	Ongoing MTX								
		+LEF (130) +PLA (133)	46 <sup>a</sup> 20	52 <sup>a</sup> 23	26 <sup>a</sup> 6	10 <sup>c</sup> 2	1.6 1.5	-0.42 <sup>a</sup> -0.09	n.d. n.d.	n.d. n.d.

R = randomized; PC = placebo controlled; BL=baseline; LOCF=last observation carried forward; n.d.=not done; LEF=leflunomide; MTX= methotrexate; PLA=placebo; SSZ=sulfasalazine

- <sup>1</sup> Intent-to-treat (ITT) population defined as all patients randomized who received at least one dose of study drug with at least 1 study evaluation. ITT subjects who did not have an evaluation after randomization (leflunomide 3, methotrexate 2, sulfasalazine 1) were not in the efficacy analysis but were in the safety analysis.
- <sup>2</sup> An ACR 20 Responder is defined by the ACR as a patient who had 20% or greater improvement in 5 of 7 core set measures of disease activity [Felson A&R 1995]. An ACR 20 Responder may also fulfill criteria for higher thresholds of response; an ACR 50 or ACR 70 Responder is defined in an analogous manner to the ACR 20 Responder, but with improvements of at least 50% or 70%, respectively.
- <sup>3</sup> An "ACR 20 Responder-at-Endpoint" is a patient who completed the study and was an ACR 20 Responder at the completion of the study. (Any patient discontinuing early was counted as a nonresponder.)

<sup>4</sup> HAQ=Health Assessment Questionnaire Disability Index (Score 0=Best, 3=Worst). A decrease in score indicates improvement.

<sup>5</sup> Retardation of structural damage compared to control was assessed using the Sharp Score [Sharp, JT. Scoring Radiographic Abnormalities in Rheumatoid Arthritis, *Radiologic Clinics of North America*, 1996; vol. 34, pp. 233-241], a composite score of erosions and joint space narrowing in hands/wrists and forefeet.

<sup>6</sup> In the publication [Smolen et al Lancet 1999], ACR20 Responder-at-Endpoint rates are given as LEF 48% and SSZ 44%, and ACR20 Responder rate for SSZ is given as 56%.

Arava or MTX or SSZ vs. placebo: <sup>a</sup>p≤0.001; <sup>b</sup>p≤0.01; <sup>c</sup>p≤0.02; <sup>d</sup>p≤0.05

Arava vs. MTX or SSZ: <sup>e</sup>p≤0.01; <sup>f</sup>p≤0.02; <sup>g</sup>p≤0.05.

[Strand V, et al. Treatment of Active Rheumatoid Arthritis with leflunomide compared with placebo and methotrexate. *Arch Intern Med* 1999;159:2542-2550; Smolen JS, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double blind, randomized, multicentre trial. *Lancet* 1999;353:259-66; Kalden JR, et al. Improved functional Ability in Patients with Rheumatoid Arthritis—longterm treatment with leflunomide versus sulfasalazine. *J Rheum* 2001;28(9): 1983-91; Emery P, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology* 2000;39:655-665; Sharp JT, et al. Treatment with leflunomide slows radiographic progression of rheumatoid arthritis. *Arthritis Rheum* 2000;43(3):495-505; Kremer JM, et al. *Annals Int Med* 2002 (in press); Kremer JM, et al. The combination of leflunomide and methotrexate in patients with active rheumatoid arthritis who are failing on MTX treatment alone: a double-blind placebo controlled study. *Arthritis Rheum* 2000; 43(9):S224; Furst DE, et al. Adding leflunomide to patients with active rheumatoid arthritis while receiving methotrexate improves physical function and health-related quality of life. *Arthritis Rheum* 2000; 43(9): S224; Arava (leflunomide) Prescribing Information Table 2 provides an overview of the Adverse Events (AEs) reported in the Phase II and III clinical trials in the 1 year database of NDA 20-905. The Arava (LEF) group includes all rheumatoid arthritis patients in the Phase II and III trials. Placebo (PLA), methotrexate (MTX), and sulfasalazine (SSZ) groups are those of the Phase III controlled trials.

<b>Table 2. Overall Summary of Adverse Events: Phase II/III NDA trials</b>				
	<b>LEF (n=1339)</b>	<b>PLA n=210)</b>	<b>MTX (n=680)</b>	<b>SSZ (n=133)</b>
	%	%	%	%
Subjects w/ 1 or more AE	83.4	82.9	92.9	91.0
Subjects w/ 1 or more drug related AE	59.8	51.4	69.7	73.7
Subjects reducing dose due to AE	4.0	0	14.1	6.8
Subjects discontinuing due to AE	15.5	7.1	13.4	22.6
Subjects w/ 1 or more SAE	22.0	10.5	21.9	16.5
Subjects w/ 1 or more drug-Related SAE	4.9	3.3	6.3	8.3

AE= adverse event; SAE= serious adverse event

In Table 3, the Phase III adverse events leading to withdrawal and serious adverse events are summarized by study and by treatment groups within each study.

<b>Table 3. Phase III Clinical Trials: Adverse Event Withdrawals and Serious Adverse Events (% of patients)</b>								
	<b>301US (12 months)</b>			<b>301MN (6 months)</b>			<b>302MN (12 months)</b>	
	<b>LEF (182)</b>	<b>PL (118)</b>	<b>MTX (182)</b>	<b>LEF (133)</b>	<b>PL (92)</b>	<b>SSZ (133)</b>	<b>LEF (501)</b>	<b>MTX (498)</b>
All AE withdrawals	22.0	8.5	10.4	14.3	6.5	18.8	18.8	14.9
Due to LFTs	7.1	1.7	4.4*	1.5	1.1	1.5	1.6	3.2
SAEs	14.8	10.2	8.2	17.3	13.0	13.5	31.1	26.9
Related	1.1	1.7	2.7	5.3	5.4	6.8	7.2	7.6
Withdrawals	3.3	1.7	3.3	5.3	3.3	3.0	9.0	5.6
Related	1.1	0.8	2.2	3.8	2.2	3.0	3.8	3.0
LFTs	0.5	0.8	1.1	0	0	0.8	0.2	0.6

LFT=liver function test

\* In the methotrexate group of the US 301 study, there were a total of 8 patients (4.4%) who withdrew due to LFT adverse events as in the study report and summary tables in the NDA Briefing Document section 6.5.3.2 and in the published manuscript [Strand V et al. *Arch Int Med* 1999; 159:2542-2550]. These include 2 patients who withdrew due to an adverse event reported as SGPT (ALT) increased and/or SGOT (AST) increased in addition to the 6 patients (3.3%) cited by HRG who withdrew due to an adverse event reported as LFT abnormal.

Table 4 summarizes the year-2 incidences of adverse event withdrawals and serious adverse events for the year-2 cohort treatment groups of the Phase III studies.

<b>Table 4. Adverse events leading to withdrawal and serious adverse events with onset in year-2</b>				
<b>Phase III studies: year-2 cohorts</b>				
	<b>% of patients</b>			
	<b>LEF (N=450)</b>	<b>SSZ (N=60)</b>	<b>MTX US301 (with folate) (N=101)</b>	<b>MTX 304 (without folate) (N=320)</b>
All AEs leading to withdrawal	4.0	13.3	7.9	4.4
SAEs	25.3	26.7	20.8	27.2
Related	3.1	8.3	2.0	1.6
Withdrawal	0.9	5.0	6.9	1.6
Related	0.4	1.7	2.0	0.6

Detailed analyses of liver enzyme elevations in the three Phase III studies of Arava monotherapy were provided in the NDA submission, including incidence and degree of elevation of both of the hepatic transaminases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). ALT is more sensitive to elevation than AST with more frequent and higher elevations, and patients in the studies with AST elevation also had ALT elevation, generally to a higher level. For that reason, ALT elevations are shown in the following tables.

<b>Table 5 –Percent of patients with ALT elevations in Phase III monotherapy trials of leflunomide: Categorized by highest elevation</b>								
	<b>LEF</b>			<b>MTX</b>		<b>PLA</b>		<b>SSZ</b>
	<b>US301 %</b>	<b>MN301/3<sup>†</sup> %</b>	<b>MN302 %</b>	<b>US301 %</b>	<b>MN302 %</b>	<b>US301 %</b>	<b>MN301 %</b>	<b>MN301/3<sup>†</sup> %</b>
<b>ALT &gt;1.2 to ≤2xULN</b>	17.6	17.3	14.4	11.0	16.9	6.8	10.9	10.5
<b>ALT &gt;2.0 to ≤3.0xULN</b>	6.6	1.5	4.4	6.6	14.9	0	0	5.3
<b>ALT &gt;3.0xULN</b>	4.4	1.5	2.6	2.7	16.7	2.5	1.1	1.5
<b>Total ALT &gt;1.2xULN</b>	28.6	18.8	21.4	20.3	48.4	9.3	12.0	14.3
<b>Total ALT &gt; 2.0xULN</b>	11.0	2.3	7.0	9.3	31.5	2.5	1.1	6.0

ULN = Upper limit of normal range.

† Includes MN303 extending the data to 12 months for the active treatment arms.

Liver enzyme elevations were generally reversible while continuing treatment or with dose reduction or discontinuation. Reversibility of clinically significant (>2xULN) ALT elevations is shown in Table 8. The table provides the number that reversed to <2x ULN and also the number that normalized to <1.2x ULN. It also states whether the normalization occurred after drug discontinuation for any reason, after dose reduction, or after no change in dose.

ALT (SGPT)	US301 <sup>1</sup> (12 mos)			MN301/303 <sup>2</sup> (12 mos)			MN302 <sup>3</sup> (12 mos)	
	LEF	PLA	MTX	LEF	PLA	SSZ	LEF	MTX
<b>&gt;3-fold ULN n(%)</b>	8 (4.4)	3 (2.5)	5 (2.7)	2 (1.5)	1 (1.1)	2 (1.5)	13(2.6)	83 (16.7)
Reversed to ≤2-xULN	8	3	5	2	1	2	12 <sup>†</sup>	82
Normalized to ≤ 1.2xULN	7	3	5	2	1	1	9	73
after discontinuation	5	2	3	1	1	1	2	23
after dose reduction	0	0	0	1	0	0	2	18
without dose change	2	1	2	0	0	0	5	32
<b>&gt;2 to ≤3x ULN n (%)</b>	12 (6.6)	0	12 (6.6)	2 (1.5)	0	7 (5.3)	22 (4.4)	74 (14.9)
Reversed to ≤2x ULN	12	-	11	2	-	6	20	70
Normalized to ≤ 1.2x ULN	10	-	9	2	-	6	19	61
after discontinuation	2	-	4	0	-	2	3	8
after dose reduction	0	-	0	0	-	2	1	12
without dose change	8	-	5	2	-	2	15	41
<b>&gt;1.2 to ≤2x ULN n (%)</b>	32 (17.6)	8 (6.8)	20 (11.0)	23 (17.3)	10 (10.9)	14 (10.5)	72 (14.4)	84 (16.9)
Reversed to ≤2x ULN	n.a. <sup>4</sup>	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Normalized to ≤1.2x ULN	31	7	16	22	9	13	71	79
after discontinuation	6	3	0	4	1	2	5	10
after dose reduction	0	0	1	0	0	0	5	4
without dose change	25	4	15	18	8	11	61	65

<sup>1</sup> Only 10% of patients in MN302 received folate. All patients in US301 received folate.

<sup>2</sup> Includes MN303 extending the data to 12 months for the active treatment arms.

<sup>3</sup> The one leflunomide-treated subject in MN302 with an elevation >3x ULN that had not reversed to <2x ULN by the end of the study subsequently reversed on followup.

<sup>4</sup> n.a. = not applicable

In year-2, both ALT elevations and abnormal LFTs reported as adverse events occurred with lower frequency compared to year-1 as shown in Table 9. Two patients had ALT elevations >3x ULN that had not reversed to <2x ULN at the end of the study, but they subsequently reversed on followup.

<b>Table 7. Clinically significant ALT elevation in year-1 and year-2: Phase III studies</b>			
	<b>% of patients</b>		
	<b>LEF ITT cohort (N=824)</b>	<b>LEF Year-2 cohort (N=450)</b>	
<b>ALT</b>			
>2 to ≤3 x ULN	4.6	5.1	2.9
>3 x ULN	3.0	2.4	1.8
<b>Abnormal LFTs reported as AEs</b>	7.8	5.6	3.3

ULN = upper limit of normal range, NA = not applicable

In the year 2 cohort a subject with an elevation in year 1 and year 2 is counted twice.

**Table 8. US4001 Liver Enzyme Elevations in Combination Therapy with Methotrexate: Month 0-6 placebo-controlled study**

<b>ALT (SGPT)</b>	<b>&gt;1.2 to ≤2x ULN n (%)</b>	<b>&gt;2 to ≤3x ULN n (%)</b>	<b>&gt;3x ULN n (%)</b>	<b>Total &gt;1.2x ULN n (%)</b>	<b>Total &gt;2x ULN n (%)</b>
<b>LEF+MTX (N=130)</b>	28 (21.5)	8 (6.2)	5 (3.8)	41 (31.5)	13 (10.0)
<b>PLA+MTX (N=133)</b>	6 (4.5)	2 (1.5)	1 (0.8)	9 (6.8)	3 (2.3)
<b>AST (SGOT)</b>					
<b>LEF+MTX (N=130)</b>	16 (12.3)	4 (3.1)	2 (1.5)	22 (16.9)	6 (4.6)
<b>PLA+MTX (N=133)</b>	5 (3.8)	0 (0.0)	1 (0.8)	6 (4.5)	1 (0.8)



## **APPENDIX C**

### **LYMPHOMA/RA CITATIONS**

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