



DEPARTMENT OF HEALTH & HUMAN SERVICES

FA-305

MAR 23 2004

Food and Drug Administration
Rockville MD 20857

MAR 24 2004 MAR 25 10 04

Sidney M. Wolfe, M.D.
Peter Lurie, M.D., M.P.H.
Elizabeth Barbehenn, Ph.D.
Public Citizen Health Research Group
1600 20th Street, N.W.
Washington, D.C. 20009-1001

Re: Docket No. 02P-0139/CP1

Dear Drs. Wolfe, Lurie, and Barbehenn:

This letter responds to your citizen petition dated March 28, 2002, regarding Arava (leflunomide tablets, 10 milligrams (mg), 20 mg, and 100 mg), marketed by Aventis Pharmaceuticals (Aventis). Your petition requests that the Food and Drug Administration (FDA) immediately remove Arava from the market because of adverse events associated with this drug. For the reasons discussed below, your petition is denied.

Conditions that would merit the withdrawal of Arava's approval are enumerated in Section 505(e) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.150 of the agency's regulations. In relevant part, these conditions include when (1) the drug presents an imminent hazard to the public health,¹ (2) available data demonstrate that the drug is unsafe or is not shown to be safe under the conditions of use upon which its marketing application was approved,² or (3) on the basis of new information and evidence available when the marketing application was approved, there is a lack of substantial evidence that the drug will have the effect it is purported or represented to have in its labeling.³ Based on the information described in this response, we have determined that these conditions do not apply. We note, however, that since the submission of your petition, Arava's labeling has been revised to further address certain hepatic and other adverse events the petition referenced. Additionally, we are continuing to monitor Arava's safety profile and to consider appropriate risk management strategies for this product.

I. BACKGROUND

FDA approved the original new drug application (NDA) for Arava (NDA 20-905) on September 10, 1998.⁴ Initially, Arava was indicated in adults to reduce signs and

¹ See 21 USC 355(e) and 21 CFR 314.150(a)(1).

² See 21 USC 355(e)(1) and (2), and 21 CFR 314.150(a)(2)(i) and (ii).

³ See 21 USC 355(e)(3) and 21 CFR 314.150(a)(2)(iii).

⁴ NDA 20-905 was submitted to FDA by Hoechst Marion Roussel, Inc., which subsequently merged with Rhône-Poulenc Rorer to create Aventis.

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symptoms of rheumatoid arthritis (RA) and to retard structural damage associated with the disease as evidenced by X-ray erosions and joint space narrowing. On June 13, 2003, Arava was approved for the further indication of improving physical function in adults with RA (NDA 20-905/S6/S7).

Since Arava was approved in 1998, its labeling has always included, among other information, several warnings and precautions regarding the drug's potential for hepatotoxicity.⁵ On June 13, 2003, FDA approved the following additional warning in Arava's labeling:

RARE CASES OF SEVERE LIVER INJURY, INCLUDING CASES WITH FATAL OUTCOME, HAVE BEEN REPORTED DURING TREATMENT WITH LEFLUNOMIDE. MOST CASES OF SEVERE LIVER INJURY OCCUR WITHIN 6 MONTHS OF THERAPY AND IN A SETTING OF MULTIPLE RISK FACTORS FOR HEPATOTOXICITY (liver disease, other hepatotoxins). (See PRECAUTIONS).

Based primarily on adverse event reports regarding hepatotoxicity, your petition contends that Arava appears more toxic than methotrexate, another drug widely used in the treatment of RA. You also submit that Arava has been associated with various other toxicities (discussed below) and is likely less efficacious than methotrexate. You further state that, in addition to methotrexate, several alternative treatments to Arava exist. For these reasons, you have requested that Arava be withdrawn from the U.S. market.

II. DISCUSSION

A. Hepatotoxicity

With regard to your contention that adverse hepatic events, including deaths, have been reported with a greater frequency for Arava than methotrexate (Petition at 1 and 7), we have carefully considered not only the information in your petition, but also other, extensive data that further illuminate this issue.⁶ These data were derived from patients

⁵ Specifically, the *Warnings* section of Arava's labeling has always (1) discussed hepatotoxicity and elevations of hepatic enzymes that occurred in clinical trials with Arava and (2) provided recommendations for enzyme monitoring and dose adjustment or discontinuation based on enzyme levels. Since Arava's 1998 approval, hepatic enzyme elevations have also been noted in the *Adverse Reactions* section of the drug's labeling. Moreover, Arava's labeled *Warnings* have always advised against use of the drug in patients with significant hepatic impairment or positive hepatitis B or C serologies. Similarly, since 1998, Arava's *Precautions* have included a statement that increased side effects may occur when the drug is given concomitantly with hepatotoxic substances, and labeling regarding Arava's *Clinical Pharmacology* has advised against the drug's use in patients with hepatic insufficiency.

⁶ As your petition does not dispute, differential reporting rates do not necessarily reflect a true increase in the risk for serious hepatic events with Arava. As the petition acknowledges, reporting rates are generally higher for relatively newly marketed drugs like Arava as compared to drugs with a longer marketing history like methotrexate. Additionally, among other issues, reporting rates may be biased due to differences in the patient populations prescribed Arava versus methotrexate (e.g., patients prescribed Arava may include individuals who are intolerant of methotrexate because, for example, of its

exposed to Arava and/or other RA therapies, including methotrexate, and encompass over 13,000 individuals exposed to Arava and over 39,000 individuals exposed to methotrexate. Along with other information, the Agency has reviewed the following:⁷

- A pooled analysis of 17 controlled clinical trials using Arava as a monotherapy (including the three pivotal trials described in Arava's approved labeling, as well as phase 2 and phase 4 studies conducted prior to and after Arava's 1998 approval). These trials included approximately 1,700 patients who were exposed to Arava and approximately 700 patients who were exposed to methotrexate
- Analyses of two phase 4 clinical trials of combination therapy involving approximately 1,200 patients exposed to Arava and 260 patients exposed to methotrexate
- Results of a postmarketing retrospective cohort study of over 40,000 RA patients, including more than 2,600 patients exposed to Arava monotherapy and more than 9,500 patients exposed to methotrexate monotherapy
- Results of a postmarketing retrospective cohort study of approximately 42,000 RA patients who received a disease-modifying antirheumatic drug, including more than 2,800 patients who received Arava and more than 19,000 patients who received methotrexate
- Postmarketing surveillance data from a national RA registry including over 5,400 patients exposed to Arava and over 10,500 patients exposed to methotrexate
- Internal and external analyses of postmarketing adverse event reports (involving hepatic events occurring both within and outside the United States), including data mining analyses of FDA's Adverse Event Reporting System (AERS).

In addition to the above, we have considered all public comments submitted regarding your petition.⁸ We also convened a meeting of our Arthritis Advisory Committee on March 5, 2003, in part to consider the safety profile of Arava. On the basis of a broad

hepatotoxicity, or may have more concomitant medications or illnesses associated with hepatotoxicity and/or because of differences in the perceived level of risk or need to report adverse events for these drugs.

⁷ Much of the data identified below are available on the Internet at <http://www.fda.gov/ohrms/dockets/ac03/briefing/3930b2.htm>. These data are also summarized in (and in many cases appended to), among other documents, a safety analysis of Arava prepared by Lawrence Goldkind, M.D. (formerly Deputy Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, Office of Drug Evaluation V, Center for Drug Evaluation and Research, FDA), that is posted on the Internet at the same Web site. Slides summarizing key data are also available on the Internet at <http://www.fda.gov/ohrms/dockets/ac/03/slides/3930s2.htm>.

⁸ Gary S. Firestein, M.D. (Professor of Medicine and Chief, Division of Rheumatology, Allergy and Immunology, University of California, San Diego School of Medicine), submitted comments dated June 10, 2002, to which you replied on October 15, 2002. On August 8, 2002, Aventis also submitted comments in response to your petition. Dr. Firestein's and Aventis' comments are posted on the Internet at <http://www.fda.gov/ohrms/dockets/ac/03/briefing/3930b2.htm>.

range of available data and information presented, including those described above, in your petition, and in presentations made by Dr. Wolfe and others at the meeting,⁹ we asked the Advisory Committee to assess the association between Arava and serious hepatotoxicity and to answer the following question: Considering the universe of available RA disease-modifying therapies, is the benefit-to-risk profile for Arava acceptable for its approved indications? The Advisory Committee voted “yes” unanimously in response to this question.^{10,11}

Based on a thorough analysis of the data presented to the Advisory Committee and all other data available to us, we agree with the Committee’s view. On the whole, existing data do not demonstrate that Arava presents a risk of hepatotoxicity severe enough to justify removing this drug from the market. Among other things:

- Available data do not demonstrate that Arava is significantly distinguished from methotrexate in terms of risk of serious hepatotoxicity
- Reported safety signals regarding hepatic failure and fatal hepatic outcomes associated with Arava do not appear to approach the magnitude of such signals associated with drugs bearing black box warnings or withdrawn from the market because of their hepatotoxicity (e.g., troglitazone, bromfenac, isoniazid, trovafloxacin)
- Reports of severe hepatic events involving Arava are rare and appropriately described in the warning that was approved for this drug on June 13, 2003 (see page 2 above)¹²

⁹ Data and information provided to the Advisory Committee are available at the Web site addresses identified in footnote 7 above. A transcript of the March 5, 2003, Advisory Committee meeting is also available on the Internet at <http://www.fda.gov/ohrms/dockets/ac/cder03.html#Arthritis>.

¹⁰ The following 12 individuals participated in this vote: Steven B. Abramson, M.D., New York University (rheumatologist) (Acting Committee Chairperson); Jennifer Anderson, Ph.D., Boston University (statistician); Kenneth D. Brandt, M.D., Indiana University (rheumatologist); Ruth S. Day, Ph.D., Duke University (consultant from FDA’s Direct Safety and Risk Management Advisory Committee); Janet D. Elashoff, Ph.D., University of California, Los Angeles (biostatistician); James F. Fries, M.D., Stanford University (rheumatologist); Allan Gibofsky, M.D., Cornell University (rheumatologist); James H. Lewis, M.D., Georgetown University (hepatologist); Robert W. Makuch, Ph.D., Yale University (biostatistician); Susan M. Manzi, M.D., University of Pittsburgh (lupologist); Wendy W. McBrair, R.N., M.S., C.H.E.S., Arthritis (Consumer Representative); and James Williams, M.D., University of Utah (rheumatologist).

¹¹ In the context of hepatotoxicity, the Arthritis Advisory Committee was also asked whether any change in labeling or other risk communication or risk management would be warranted for the optimal safe use of Arava. Although Committee members who commented on this question did not believe that a labeling or other change was warranted based on available data, we subsequently approved the warning statement regarding severe liver injury reproduced on page 2 above.

¹² This warning is consistent with information about liver injuries in a public statement issued by the European Agency for the Evaluation of Medicinal Products (EMEA) that is referenced in your petition. See EMEA Public Statement on leflunomide (Arava) – Severe and Serious Hepatic Reactions (March 12, 2001). Although this statement warns of severe hepatic events associated with the use of Arava, the EMEA has not sought to remove this drug from the European market.

- The overall risk of hepatotoxicity known to be associated with Arava is consistent with the drug's currently approved labeling.

In light of the above, your request that Arava be withdrawn from the U.S. market because of its hepatotoxicity is denied.

B. Other Adverse Effects and Safety Factors

1. Non-Hepatic Adverse Effects

As noted above, in addition to hepatotoxicity, your petition states that other toxicities have been associated with Arava in premarketing studies and/or postmarketing adverse event reports, including hypertension, Stevens-Johnson Syndrome, leucocytoclastic vasculitis, lymphoma, pregnancy-related complications, including male-mediated (testicular) toxicity, pancytopenia, thrombocytopenia, diarrhea, and weight loss (Petition at 1 to 2 and 8 to 13).

We note that several of the conditions you describe are known risks that are disclosed in Arava's current labeling.¹³ For example, Arava is contraindicated in pregnant women and women of childbearing potential who are not using reliable contraception. Arava's labeling also includes a black box warning that directs that pregnancy must be avoided during treatment with this drug. Similarly, Arava's labeled *Warnings* address instances of Stevens-Johnson Syndrome, pancytopenia, and thrombocytopenia¹⁴, as well as the risk of malignancy, particularly lymphoproliferative disorders.¹⁵ Additionally, hypertension,

¹³ Some such risks have been disclosed since Arava's 1998 approval; as noted above, others have been added to the label subsequently, including after the submission of your petition.

¹⁴ Regarding pancytopenia and thrombocytopenia, your petition asserts that Arava's labeling merely advises that patients taking other immunosuppressive agents should use the drug "with caution" and obtain "frequent clinical and hematological monitoring." (Petition at 12) In fact, Arava's current labeling includes strengthened warnings regarding these risks:

There have been rare reports of pancytopenia, agranulocytosis and thrombocytopenia in patients receiving ARAVA alone. These events have been reported most frequently in patients who received concomitant treatment with methotrexate or other immunosuppressive agents, or who had recently discontinued these therapies; in some cases, patients had a prior history of a significant hematologic abnormality. Patients taking ARAVA should have platelet, white blood cell count and hemoglobin or hematocrit monitored at baseline and monthly for six months following initiation of therapy and every 6- to 8 weeks thereafter. If used with concomitant methotrexate and/or other potential immunosuppressive agents, chronic monitoring should be monthly. If evidence of bone marrow suppression occurs in a patient taking ARAVA, treatment with ARAVA should be stopped, and cholestyramine or charcoal should be used to reduce the plasma concentration of leflunomide active metabolite (see PRECAUTIONS – General – Need for Drug Elimination).

¹⁵ On this point, your petition asserts that Arava's labeling merely warns of the drug's potential for immunosuppression without addressing lymphoma (Petition at 9). In fact, current Arava labeling specifically states in part that, "The risk of malignancy, particularly lymphoproliferative disorders, is increased with the use of some immunosuppression medications. There is a potential for immunosuppression with ARAVA."

diarrhea, and weight loss are disclosed in the *Adverse Events* section of current Arava labeling.

Based on a careful review of the information you provided, as well as other data available to us, we have determined that current information and data do not reveal changes in the established risks of the toxicities above that merit withdrawing Arava from the market.¹⁶

With regard to male-mediated fetal toxicity, you assert that Arava's labeling "does not provide information on" this risk (Petition at 10). However, the labeling's current *Precautions* section in fact addresses this subject. While you contend that certain animal (dog) data suggest such toxicity, as this section explains, we have determined that the full range of "[a]vailable information does not suggest that Arava would be associated with an increased risk of male-mediated fetal toxicity."

You also challenge Arava's safety on grounds that genotoxicity testing was performed on the parent drug only and not its major active metabolite (Petition at 9). This contention is wrong. In accordance with general practice, Arava's genotoxicity evaluation included tests performed on the parent drug alone as well as on metabolites produced after exposure of the parent drug to liver enzymes. As demonstrated by *in vitro* and *in vivo* metabolism data included in its NDA, Arava is readily metabolized into its major active metabolite (A771726 or M1) by liver enzymes. Therefore, this metabolite (as well as the parent drug) was in fact assessed in Arava's genotoxicity testing.

You further assert that one of Arava's minor metabolites, trifluoromethyl aniline (TFMA), is a potent genotoxin (Petition at 9). Although, as you indicate and as disclosed in Arava's current labeling, TFMA demonstrated genotoxicity in certain testing (*in vitro* Chinese hamster and bacterial assays), it has shown no genotoxicity in *in vivo* testing.¹⁷ Moreover, little or no TFMA has been formed in *in vitro* tests involving human and rat microsomal enzymes, and, as noted in current labeling, TFMA has been found in human plasma only infrequently and at low levels. Based on all available data, we have determined that concerns about TFMA's genotoxicity do not support withdrawing Arava from the market.

2. Long half-life

As your petition notes, Arava is quickly metabolized to M1 after oral administration. As explained in Arava's labeling, M1 has a long half-life (in general, approximately 2 weeks). You maintain that this long half-life contributes to Arava's toxicity (Petition at

¹⁶ Much of the data available to us regarding these adverse events, and an assessment thereof, are included in Dr. Lawrence Goldkind's Arava safety analysis posted on the Internet at the Web site address identified in footnote 7.

¹⁷ As the *Precautions* section of current Arava labeling explains, "[TFMA], a minor metabolite of leflunomide, was mutagenic in the Ames Assay and in the HGPRT Gene Mutation Assay, and was clastogenic in the *in vitro* Assay for Chromosome Aberrations in the Chinese Hamster Cells. TFMA was not clastogenic in the *in vivo* Mouse Micronucleus Assay nor in the *in vivo* Cytogenetic Test in Chinese Hamster Bone Marrow Cells."

14).¹⁸ Specifically, you assert that labeling suggesting that women should wait two years after Arava treatment before attempting to conceive “impl[ies] that there are body depots where [M1] remains for many months.” (Petition at 14) This contention is wrong. The two-year time period was calculated to reflect an extreme, worst-case scenario for drug elimination and does not represent a typical time period that M1 is likely to be retained. In fact, the two-year period exceeds the retention period that would be expected based on the longest half-life observed in Arava’s population pharmacokinetics database; we lengthened the retention period expected based on the longest half-life observed to create an added margin of safety. Moreover, the two-year time period does not account for use of the enhanced drug elimination procedures recommended in Arava’s labeling. As the labeling indicates, if these procedures are followed, M1 plasma levels can be sharply diminished below detectable levels within two weeks of Arava’s discontinuation.¹⁹ This rapid diminishment belies your claim that M1 remains in body depots for many months. The elimination agents recommended in Arava’s labeling (discussed below) interrupt the recycling (i.e., continued elimination and re-absorption) of M1 that occurs in the gastrointestinal tract. It is this recycling that accounts for M1’s long half-life. If M1’s half-life were attributable to its retention in body depots, the recommended elimination agents would not be expected to have much, if any, effect.

You also claim that, because of its longer half-life, the average length of time required to attain steady-state plasma levels for M1 (10 to 12 weeks) is much longer than for methotrexate (1 to 2.5 days) (Petition at 14). You further contend that the time required to attain steady-state plasma levels reflects the time expected for a drug to disappear from the body once it is discontinued (Petition at 14). These contentions are misleading. The 10 to 12 week period you cite represents the average time expected to achieve steady-state M1 plasma levels in the absence of a loading dose. Because of M1’s half-life, the *Dosage and Administration* section of Arava’s labeling advises that therapy with this drug be initiated using a loading dose (one 100 mg tablet per day for three days) to expedite the attainment of steady-state concentrations.²⁰ Similarly, as earlier noted, Arava’s labeling recommends the use of enhanced elimination (i.e., washout) procedures to hasten the depletion of M1 plasma levels upon Arava’s discontinuation. These procedures are further discussed below.

Finally, you submit that gender, age, and smoking all influence M1 plasma levels but that Arava’s labeling identifies only smoking as a significant factor (Petition at 14). Although you cite certain clinical data in the pharmacology review for Arava in support of your contention, your sole reliance on this data is selective and misleading. When all available data are considered (including population pharmacokinetic data consisting of more than

¹⁸ Your petition comments that animal data on M1’s half-life were not included in the drug’s NDA review or were not available to you (Petition at 14). In fact, animal data are included in Arava’s pharmacology review, which is available on the Internet at http://www.fda.gov/cder/foi/nda/98/20905_arava.htm.

¹⁹ Drug elimination procedures are described in the *Warnings* section of current Arava labeling.

²⁰ The *Clinical Studies* section of Arava’s labeling also explains that, “In all Arava monotherapy studies, an initial loading dose of 100 mg per day for three days only was used followed by 20 mg per day thereafter.”

10,000 plasma samples from over 742 patients), “[n]either age nor gender has been shown to cause a consistent change in the in vivo pharmacokinetics of M1.”²¹

For the reasons described above, your contentions regarding M1’s half-life do not support Arava’s market withdrawal.

3. Washout Procedures

Along with challenging its half-life, you assert that the washout procedures recommended in labeling to facilitate M1’s elimination (use of cholestyramine or charcoal) were inadequately tested. In particular, you contend that cholestyramine and charcoal were tested in patients who received only one 20 mg or 100 mg dose of Arava, as opposed to patients who had been taking Arava for 10 to 12 weeks, which you maintain is the time needed to reach steady-state M1 plasma levels (Petition at 14 to 15). You also maintain that charcoal was tested in only one healthy subject (Petition at 15). These claims are incorrect.

Studies evaluating the effectiveness of both cholestyramine and charcoal as washout agents were not limited to subjects who had received only a single 20 mg or 100 mg dose of Arava. On the contrary, both of these agents were tested for effectiveness in subjects who had been administered a loading dose of Arava (100 mg a day for 3 days), followed by a planned clinical dose. As discussed above, the administration of a loading dose expedites the attainment of steady-state plasma drug levels and eliminates the 10 to 12 week period otherwise needed, on average, to achieve such levels.

Your statement that charcoal was evaluated in only one healthy subject is similarly inaccurate. Cholestyramine and charcoal were both evaluated in multiple subjects. As Arava’s current labeling notes, “Administration of cholestyramine or activated charcoal in patients (n=13) and volunteers (n=96) resulted in a rapid and significant decrease in plasma M1 (the active metabolite of leflunomide) concentration....”²²

In summary, for the reasons stated above, we have concluded that your arguments regarding Arava’s non-hepatic adverse effects, active metabolite half-life, and recommended washout procedures do not support withdrawing this drug from the market.

C. Effectiveness

In addition to questioning Arava’s safety profile, your petition contends that Arava is likely less effective than methotrexate for the treatment of RA (Petition at 2). You cite the results from Aventis’ MN302 phase 3 study (ACR 20 Responder at Endpoint rate of 43 percent with Arava versus 57 percent with methotrexate, $p \leq 0.0001$) in support of this contention (Petition at 3). However, the results of MN302 are likely affected by the fact that 90 percent of the patients receiving methotrexate in this study were not administered

²¹ Current Arava labeling, *Clinical Pharmacology* section.

²² Current Arava labeling, *Precautions* section.

folate. Standard clinical practice in the U.S. is for folate to be administered concomitantly with methotrexate. As your petition acknowledges, folate reduces much of the toxicity of methotrexate; however, it is also thought to reduce methotrexate's efficacy.²³ We have considered this and other relevant information regarding MN302, as well as other available clinical data, including data comparing Arava and methotrexate when administered in conjunction with folate. Based on this review, we have concluded that (1) available data do not demonstrate consistent differences in the effectiveness of Arava and methotrexate, particularly when these drugs are administered in accordance with standard U.S. clinical practice (i.e., when methotrexate is administered with folate), and (2) in any event, Arava is effective for its approved RA indications.

You further contend that the continued marketing of Arava cannot be justified because, in addition to methotrexate, there are several alternate RA treatments (Petition at 3, 17 to 18, and 19). The fact that methotrexate and other effective RA treatments exist does not support discontinuing Arava's availability. RA is a chronic, progressive disease with debilitating effects and no known cure. Through our experience evaluating RA drug therapies, we are aware that despite their benefits, all such therapies are associated with serious toxicities and none is universally effective or well tolerated. We are further aware that significant numbers of RA patients require a variety of treatment options during extended periods of treatment for this disease. For these reasons, and in light of the safety and effectiveness information discussed earlier in this letter, we conclude that Arava's continued availability is important and justified.

III. CONCLUSION

As discussed above, we have thoroughly evaluated the extensive data available to us regarding Arava. On the basis of this review, we have determined that, on the whole, these data do not demonstrate that Arava presents a risk of serious hepatotoxicity or other toxicity severe enough, or that it is insufficiently effective, to justify removing this drug from the market.²⁴ We will continue to evaluate Arava's risk-benefit profile as new information becomes available and will take appropriate regulatory action as needed. However, as explained above, currently available scientific information does not support

²³ See, e.g., Hoekstra M, van Ede AE, Haagsma CJ, et al., "Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis," *Ann Rheum Dis*. 2003 May; 62(5):423-6; van Ede AE, Laan RF, Rood MJ, et al., "Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight week, multicenter, randomized, double-blind, placebo-controlled study," *Arthritis Rheum*. 2001 Jul; 44(7):1515-24; Ortiz Z, Shea B, Suarez Almazor M, et al., "Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis," *Cochrane Database Syst Rev*. 2000; 2:CD000951.

²⁴ Your petition submits that *Dear Doctor* letters or black box warnings would not be effective alternatives to withdrawing Arava from the U.S. market (Petition at 18 to 19). As explained above, we have determined that the totality of existing data does not support your withdrawal request. Thus, this letter does not address the appropriateness of labeling changes as an alternative to market withdrawal.

the action you requested. Therefore, your petition is denied.

Sincerely,

A handwritten signature in black ink, appearing to read 'S. Galson', written in a cursive style.

Steven K. Galson, M.D., M.P.H.
Acting Director
Center for Drug Evaluation and Research