DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE **March 28, 2006**

Susan Vermeir
Vice President, Regulatory Affairs
InterMune, Inc.
3280 Bayshore Blvd.
Brisbane, CA 94005

RE: BLA # 103663
INFERGEN® (Interferon alfacon-1)
MACMIS ID # 14068

Dear Ms. Vermeir:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a journal advertisement (journal ad) (IFN146.US) with Brief Summary (IFN147.US) for Infergen® (Interferon alfacon-1) submitted by InterMune, Inc. (InterMune) under cover of Form FDA 2253. The journal ad is false or misleading because it overstates efficacy and omits and minimizes information on the risks associated with Infergen. Therefore, the journal ad misbrands Infergen in violation of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§352(n) & 321(n), and FDA implementing regulations, 21 CFR §§202.1(e)(5) and (6). These violations concern us from a public health perspective because they suggest that Infergen is more effective and safer than has been demonstrated.

Background

The Indications and Usage section of the FDA-approved product labeling (PI) for Infergen states:

> INFERGEN is indicated for the treatment of chronic HCV infection in patients 18 years of age or older with compensated liver disease who have anti-HCV serum antibodies and/or the presence of HCV RNA. Other causes of hepatitis, such as viral hepatitis B or autoimmune hepatitis, should be ruled out prior to initiation of therapy with INFERGEN. In some patients with chronic HCV infection, INFERGEN normalizes serum ALT, reduces serum HCV RNA concentrations to undetectable quantities (<100 copies/mL), and improves liver histology.

In the section of the PI entitled "Clinical Experience: Response to Infergen," the subsection entitled "Subsequent Treatment" states, in relevant part:

> Subsequent treatment with 15 mcg of INFERGEN for 24 and 48 weeks was evaluated in an open-label clinical trial in 208 patients who had failed initial therapy for 24 weeks with either 9

mcg INFERGEN or 3 MIU (approximately 15 mcg) IFN α-2b. Of these patients, 133/208 had failed to normalize ALT during the initial treatment period. Seventy-five of 208 achieved normal ALT during initial treatment, but experienced relapse (return of abnormal ALT) during posttreatment observation. Patients were assessed for normalization of ALT (ALT response rate) and HCV RNA reduction to less than 100 copies/mL (HCV response rate) at the end of 24 weeks of observation following discontinuation of therapy. Sustained response rates measured by ALT normalization and HCV RNA reductions to below detectable limits for patients who received subsequent treatment with 15 mcg of INFERGEN are included in Table [1].

Table [1]. Sustained Response Rates (95% CI) of ALT Normalization and HCV RNA Reductions to Below Detectable Limits After Subsequent Treatment[b] with 15 mcg INFERGEN

All Patients		Prior Nonresponders		Prior Relapsers	
24 Weeks n=107	48 Weeks n=101	24 Weeks n=74	48 Weeks n=59	24 Weeks n=33	48 Weeks n=42
End of Observation Normalized ALT					
13% (7.3%, 21.0%)	19% (11.7%, 27.8%)	7% (2.2%, 15.1%)	7% (1.9%, 16.5%)	27% (13.3%, 45.5%)	36% (21.6%, 52.0%)
End of Observation HCV RNA Negative					
9% (4.6%, 16.7%)	22% (13.4%, 30.0%)	4% (0.9%, 11.5%)	12% (4.9%, 22.9%)	21% (9.0%, 38.9%)	36% (21.6%, 52.0%)

a. P value=0.01.
b. Subsequent treatment data are presented for patients initially treated with 9 mcg INFERGEN or 3 MIU IFN α-2b in the initial treatment study; patients initially treated with 3 mcg INFERGEN were excluded from this analysis.

The Dosage and Administration section of the PI provides the following information in relevant part:

> Patients who tolerated previous interferon therapy and did not respond or relapsed following its discontinuation may be subsequently treated with 15 mcg of INFERGEN TIW administered SC as a single injection for up to 48 weeks.....

Furthermore, according to the PI, Infergen is associated with several risks, including the following Warnings (in pertinent part):

> Boxed Warning:
>
> > Alpha interferons, including interferon alfacon-1, cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders.
> >
> > Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening symptoms of these conditions should be withdrawn from therapy. In many but not all cases, these disorders resolve after stopping Interferon alfacon-1 therapy.

See WARNINGS, and ADVERSE REACTIONS.

SEVERE PSYCHIATRIC ADVERSE EVENTS MAY MANIFEST IN PATIENTS RECEIVING THERAPY WITH ALPHA INTERFERON, INCLUDING INFERGEN. DEPRESSION, SUICIDAL IDEATION, AND SUICIDE ATTEMPT MAY OCCUR. The incidence of psychiatric events of suicidal ideation and attempts was small (1%) for patients treated with 9 mcg INFERGEN compared to the overall incidence (55%) of psychiatric events. INFERGEN should be used with caution in patients who report a history of depression and physicians should monitor all patients for evidence of depression. Physicians should inform patients of the possible development of depression prior to initiation of INFERGEN therapy, and patients should report any sign or symptom of depression immediately. Other prominent psychiatric adverse events may also occur, including nervousness, anxiety, emotional lability, abnormal thinking, agitation, or apathy . . . .

INFERGEN SHOULD BE ADMINISTERED WITH CAUTION TO PATIENTS WITH PRE-EXISTING CARDIAC DISEASE. Hypertension and supraventricular arrhythmias, chest pain, and myocardial infarction have been associated with alpha interferon therapies.

Bone Marrow Toxicity: Alpha interferons suppress bone marrow function and may result in severe cytopenias including very rare events of aplastic anemia. It is advised that complete blood counts be obtained pretreatment and monitored routinely during therapy. Alpha interferon therapy should be discontinued in patients who develop severe decreases in neutrophil ($< 0.5 \times 10^9$/L) or platelet counts ($< 50 \times 10^9$/L).

Ophthalmologic Disorders: Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein thrombosis, retinal hemorrhages and cotton wool spots; optic neuritis, and papilledema are induced or aggravated by treatment with Interferon alfacon-1 or other alpha interferons. All patients should receive an eye examination at baseline. Patients with preexisting ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during interferon alpha treatment. Any patient who develops ocular symptoms should receive a prompt and complete eye examination. Interferon alfacon-1 therapy should be discontinued in patients who develop new or worsening ophthalmologic disorders.

Overstatement of Efficacy

The journal ad claims that "Only Infergen offers a proven treatment option for the significant and growing number of nonresponders and relapsers," referring to patients with chronic hepatitis C virus (HCV) infection who do not respond to or who relapse following initial drug treatment, and cites a publication by Heathcote, et.al.[1] as support for the claim. The article by Heathcote, et.al., published in 1998, as well as the Infergen PI, report the results of studies that assessed the effect of the product in patients who did not respond to or who relapsed after initial regimens consisting only of non-pegylated

[1] Heathcote EJ, Keeffe EB, Lee SS, et al. Re-treatment of chronic hepatitis C with consensus interferon. Hepatology. 1998;27:1136-1143.

interferons (interferon α-2b or Infergen 9 mcg) without ribavirin. We note that the dosing information provided in the PI for nonresponders and relapsers is also based on patients who were initially treated with these non-pegylated regimens. Accordingly, all the study data on which your claim is based involve treatment with Infergen after the initial failure of specific, older regimens. Since 1998, however, a number of new regimens that consist of a pegylated interferon alfa in combination with ribavirin have been approved and emerged as the new standard of care. By failing to point this out, the journal ad misleadingly implies that Infergen has been proven safe and effective for the treatment of patients who have failed these newer regimens. However, FDA is unaware of substantial evidence or substantial clinical experience that supports the safety and efficacy of Infergen in the treatment of HCV-infected patients who have failed newer initial treatments. In the absence of this evidence or additional contextual information in the journal ad explaining the frame of reference of the Heathcote study, the representation in the ad is misleading.

While we note that a second citation - to "data on file" -- is included in the brief summary portion of the ad to support the claim, this citation does not address our concern. Instead, the data on file that we received from you in response to our request for this information relates to another portion of the claim - that the population of nonresponders and relapsers is increasing.

Omission/Minimization of Important Risk Information

Prescription drug advertisements are false or misleading if they fail to reveal facts that are material in light of the representations made in the advertisements or with respect to the consequences that may result from the use of the drug as recommended or suggested in the advertisements. We note the presentation of the boxed warning, which broadly serves to highlight that there are serious risks associated with Infergen therapy, such as fatal or life-threatening neuropsychiatric and ischemic disorders. However, the journal ad fails to present an important warning concerning the need for caution when administering the drug to patients with pre-existing cardiac disease due to the risk of hypertension, supraventricular arrhythmias, chest pain, and myocardial infarction. The journal ad also omits warnings related to bone marrow suppression and ophthalmologic disorders. In addition, notwithstanding the presentation of the boxed warning, the ad fails to present specific information from the warnings section related to the risk of severe psychiatric adverse events, thereby minimizing the risk of suicide attempt, suicidal ideation, and depression. By omitting and minimizing this important risk information, the ad misleadingly suggests that Infergen is safer than has been demonstrated.

Conclusion and Requested Action

For the reasons discussed above, your journal advertisement overstates the efficacy of Infergen and omits and minimizes important risk information associated with the drug. Therefore, the journal ad misbrands Infergen in violation of the Act and FDA implementing regulations. See 21 U.S.C. §§352(n) & 321(n) and 21 CFR §§202.1(e)(5) and (6).

DDMAC requests that InterMune immediately cease the dissemination of violative promotional materials for Infergen such as those described above. Please submit a written response to this letter on or before April 11, 2006, stating whether you intend to comply with this request, listing all violative promotional materials for Infergen such as those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug

Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705, facsimile at 301-796-9878. In all future correspondence regarding this matter, please refer to MACMIS ID # 14068 in addition to the BLA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Infergen comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

Lynn Panholzer, PharmD
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications