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Food and Drug Administration  
Rockville, MD 20857

**TRANSMITTED VIA FACSIMILE**

Adrain Adams  
President  
Kos Pharmaceuticals, Inc.  
1001 Brickell Bay Drive, Suite 2500  
Miami, Florida 33131

JUL 13 2001

**RE: NDA #20-381  
Niaspan (niacin extended-release) Tablets  
MACMIS ID# 10125**

**WARNING LETTER**

Dear Mr. Adams:

This Warning Letter concerns Kos Pharmaceuticals, Inc.'s (Kos), direct-to-consumer print advertisement for Niaspan (niacin extended-release) tablets, which appeared in the June 11, 2001, issue of *Time*. The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed this magazine advertisement as part of its routine monitoring and surveillance program. DDMAC has concluded that Kos' advertisement is false, lacking in fair balance, or otherwise misleading in violation of the Federal Food, Drug, and Cosmetic Act (Act), and applicable regulations (See 21 U.S.C. §§ 331(a) and (b), 352 (n)).

Your direct-to-consumer advertisement for Niaspan, disseminated in *Time*, a widely read publication, fails to present significant risks associated with Niaspan therapy. Your advertisement also contains misleading efficacy claims and implies a use for Niaspan that is inconsistent with the approved product labeling (PI). As a result, your advertisement raises significant public health and safety concerns.

**Background**

Niaspan was approved in 1997. As specified in the PI, niacin therapy is indicated as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate. Specifically, Niaspan is indicated as monotherapy (as an adjunct to diet) to reduce elevated TC, LDL-C, Apo B, and TG levels, and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia. Niaspan is also indicated as

combination therapy with a bile acid binding resin to reduce elevated TC and LDL-C levels in adult patients with primary hypercholesterolemia, and to slow progression or promote regression of atherosclerotic disease in patients with a history of coronary artery disease (CAD) and hypercholesterolemia. In addition, Niaspan is indicated to reduce the risk of recurrent nonfatal myocardial infarction (MI) in patients with a history of MI and hypercholesterolemia.

Niaspan is also associated with significant risks. Niaspan is contraindicated in patients with significant or unexplained hepatic dysfunction, active peptic ulcer disease, or arterial bleeding. The PI for Niaspan includes bolded warnings concerning: the occurrence of severe hepatic toxicity, including fulminant hepatic necrosis, in patients who substituted sustained-release niacin products for immediate-release niacin products at equivalent doses; and the cautious use of Niaspan in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. In addition, the PI contains a warning regarding rhabdomyolysis when niacin is used together with HMG-CoA reductase inhibitors.

### **Lacking in Fair Balance**

Prescription drug advertisements lack fair balance if they fail to present the information relating to contraindications, warnings, precautions, and side effects associated with the use of a drug with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of the drug.

Your advertisement fails to present significant risks associated with Niaspan therapy. Specifically, your advertisement omits the bolded warning concerning the potential for severe hepatic toxicity, including fulminant hepatic necrosis, when substituting Niaspan for equivalent doses of immediate-release niacin products. Your advertisement also omits the bolded warning concerning the cautious use of Niaspan in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Furthermore, although your advertisement promotes the concomitant use of niacin with simvastatin (a HMG-CoA reductase inhibitor), it fails to mention that the combined use of niacin and simvastatin may cause rhabdomyolysis. All of these serious risks are prominently presented in the PI, with specific information on the need for dosage adjustments, liver function testing, and symptomatic monitoring to avoid such potentially fatal outcomes.

Your advertisement states that "In extensive clinical studies the most common side effect was flushing which was usually temporary." This statement minimizes the significant impact of flushing, which was reported by as many as 88% of patients taking Niaspan in placebo-controlled trials, and is very bothersome to many patients. In addition, this statement does not define flushing for the target audience. Unless a consumer has experienced a niacin-related flushing episode, the term "flushing" will suggest an embarrassment reaction, not the uncomfortable warmth, redness, itching, and/or tingling that comprise the experience with Niaspan, and is described in the PI.

The presentation of the risk information you chose to include further minimizes the significance of Niaspan's risks. Your ad presents this information in the bottom left corner, in very small type size and block paragraph format. The manner of this presentation is not reasonably comparable, in either readability or prominence, to your advertisement's presentation of Niaspan's effectiveness, which includes charts, large and bold type size, and effective use of white space.

### **False or Misleading Efficacy Presentation**

Prescription drug advertisements are false or misleading if they suggest that a drug is better, more effective, or useful in a broader range of conditions or patients than has been demonstrated by substantial evidence.

First, your advertisement misleadingly implies that Niaspan can prevent heart attacks in patients with or without a history of MI who have normal LDL cholesterol. Your advertisement does this by presenting the large, bolded headline "What you don't know about cholesterol might shock you. Heart attacks happen to many people with normal LDL cholesterol levels." However, Niaspan is not indicated to reduce the risk of heart attacks in patients with normal LDL cholesterol. It is indicated "to reduce the risk of recurrent nonfatal myocardial infarction" only in patients "with a history of myocardial infarction and hypercholesterolemia" [emphasis added].

Second, your advertisement misleadingly implies that Niaspan can significantly reduce cardiac events by raising HDL cholesterol. Your advertisement does this by presenting the claims "Recent clinical studies demonstrate raising HDL, good cholesterol, can significantly reduce cardiac events," "...lowering your 'bad' LDL cholesterol may not be enough to prevent heart disease," and "Today, more and more heart specialists are doing more by helping their patients raise 'good' HDL cholesterol." However, the Clinical Pharmacology section of Niaspan's PI specifically states that "the independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined."

Finally, your advertisement misleadingly implies that Niaspan is indicated as adjunctive therapy with simvastatin for a reduction in cardiac events. Your advertisement does this by presenting the claim "Your next step for greater risk reduction" along with a graphic presenting "HDL" and "Cardiac Events Reduced" for simvastatin and simvastatin + niacin. This graphic highlights how the addition of niacin to simvastatin reduces cardiac events by 70%, compared with simvastatin monotherapy that only shows a 34% reduction. The PI for Niaspan describes the concomitant use of niacin and HMG-CoA reductase inhibitors, such as simvastatin, on lipid parameters. However, Niaspan is not indicated for concomitant use with simvastatin to reduce the risk of cardiac events. Further, you have not provided substantial evidence in the form of adequate and well-

controlled, head-to-head, clinical trials to support the claim that adding Niaspan to simvastatin will reduce cardiac events more than using simvastatin alone.

### **Misleading Communication of Indication**

Your advertisement presents the claim "Prescription NIASPAN is indicated as an adjunct to diet and exercise." However, this statement does not accurately communicate to the consumer the limitations to the indication. Specifically, the PI states, "Niacin therapy is indicated as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate" [emphasis added].

### **Failure To Submit Post-Marketing Reports**

Finally, although this advertisement was disseminated in the June 11, 2001, issue of *Time*, you have failed to submit it at the time of initial publication as required under the post-marketing reporting requirements (21 CFR 314.81(b)(3)(i)).

### **Conclusions and Requested Actions**

You have disseminated a direct-to-consumer magazine advertisement that lacks fair balance and contains false or misleading claims and presentations. Because of the significant public health and safety concerns raised by your advertisement, we request that you provide a detailed response to the issues raised in this Warning Letter. This response should contain an action plan that includes:

- 1) Immediately ceasing the dissemination of this advertisement and all promotional materials that contain the same or similar violations outlined in this letter.
- 2) Providing a plan of action to disseminate accurate and complete information to the audience(s) that received the misleading messages.
- 3) A written statement of your intent to comply with "1" and "2" above.

You should respond in writing to DDMAC by July 27, 2001, of your intent to comply with DDMAC's request. If Kos has any questions or comments, please contact Andrew Haffer, Pharm.D. or Jean-Ah Choi, Pharm.D. by facsimile at 301-594-6771 or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857.

We remind you that only written communications are considered official. In all future correspondence regarding this particular matter, please refer to MACMIS ID #10125 in addition to the NDA number.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of your promotional campaign for Niaspan, and may determine that additional remedial messages will be necessary to fully correct the false or misleading messages resulting from your violative conduct.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

*{See appended electronic signature page}*

Thomas W. Abrams, R.Ph., MBA  
Director  
Division of Drug Marketing,  
Advertising, and Communications

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Thomas Abrams

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