DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

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 recurrrent 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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

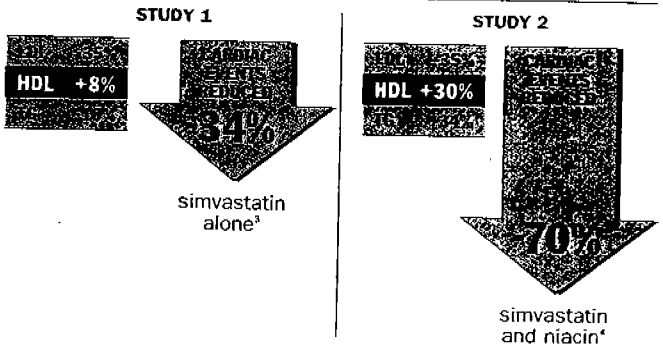
/s/

Thomas Abrams
7/13/01 01:56:43 PM

What you don't know about CHOLESTEROL might shock you.

Heart attacks happen to many people with normal LDL cholesterol levels.[1,2]

Recent clinical studies demonstrate raising HDL, good cholesterol, can significantly reduce cardiac events.



That's right. Recent studies show that lowering your "bad" LDL cholesterol may not be enough to prevent heart disease. Today, more and more heart specialists are doing more by helping their patients raise "good" HDL cholesterol. Ask your doctor if NIASPAN® (niacin extended-release tablets) is right for you.

To request information about NIASPAN® call 1-888-5-NIASPAN.

Your next step for greater risk reduction

PRESCRIPTION NIASPAN® *niacin* EXTENDED-RELEASE TABLETS

Prescription NIASPAN® is indicated as an adjunct to diet and exercise. But it's not for everybody. People with liver problems, active peptic ulcers, or arterial bleeding should not take NIASPAN®. In extensive clinical studies the most common side-effect was flushing which was usually temporary. You should tell your doctor if you experience dizziness. If diabetic, notify your doctor of changes in blood glucose. Please see the brief summary on the following page.

KOS

Good Medicine for Good Cholesterol

REFERENCES: **1** Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med.* 1999;341:410-418. **2** Robins SJ, Collins D, Wittes JT, et al. Relation of gemfibrozil treatment and lipid levels with major coronary events. VA-HIT: A randomized controlled trial. *JAMA.* 2001;285:1585-1591. **3** Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet.* 1994;344:1383-1389. **4** Brown G, Zhao X, Chait A, et al. Niacin plus simvastatin, but not antioxidant vitamins, protect against atherosclerosis and clinical events in CAD patients with low HDL-C. Abstract presented at *73rd AHA Scientific Sessions, New Orleans, LA,* 2000 Nov 13.

NIASPAN® Rx Only
niacin extended-release tablets

Brief Summary of Prescribing Information

INDICATIONS AND USAGE: 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 (see also the NCEP treatment guideline[1]).

1. NIASPAN is indicated as an adjunct to diet for reduction of elevated TC, LDL-C, Apo B and TG levels, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson Types IIa and IIb), when the response to an appropriate diet has been inadequate.
2. In patients with a history of myocardial infarction and hypercholesterolemia, niacin is indicated to reduce the risk of recurrent nonfatal myocardial infarction.
3. In patients with a history of coronary artery disease (CAD) and hypercholesterolemia, niacin, in combination with a bile acid-binding resin, is indicated to slow progression or promote regression of atherosclerotic disease.
4. NIASPAN in combination with a bile acid-binding resin is indicated as an adjunct to diet for reduction of elevated TC and LDL-C levels in adult patients with primary hypercholesterolemia (Type IIa), when the response to an appropriate diet, or diet plus monotherapy, has been inadequate.

Niacin is also indicated as adjunctive therapy for treatment of adult patients with very high serum TG levels (Types IV and V hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them.

Your next step for greater risk reduction

PRESCRIPTION NIASPAN® niacin EXTENDED-RELEASE TABLETS

CONTRAINDICATIONS: NIASPAN is contraindicated in patients with a known hypersensitivity to niacin or any component of this medication, significant or unexplained hepatic dysfunction, active peptic ulcer disease, or arterial bleeding.

WARNINGS: NIASPAN preparations should not be substituted for equivalent doses of immediate-release (crystalline) niacin. For patients switching from immediate-release niacin to NIASPAN, therapy with NIASPAN should be initiated with low doses (i.e., 500 mg qhs) and the NIASPAN dose should then be titrated to the desired therapeutic response (see DOSAGE AND ADMINISTRATION in full prescribing information).

***Liver Dysfunction*—Cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have substituted sustained-release (modified-release, timed-release) niacin products for immediate-release (crystalline) niacin at equivalent doses.**

NIASPAN should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of NIASPAN.

Niacin preparations, like some other lipid-lowering therapies, have been associated with abnormal liver tests. In three placebo-controlled clinical trials involving titration to final daily NIASPAN doses ranging from 500 to 3000mg, 245 patients received NIASPAN for a mean duration of 17 weeks. No patient with normal serum transaminase levels (AST, ALT) at baseline experienced elevations to more than 3 times the upper limit of normal (x ULN) during treatment with NIASPAN. In these studies, fewer than 1% (2/245) of NIASPAN patients discontinued due to transaminase elevations greater than 2x ULN.

Interim results from a recently completed, long-term extension study involving more than 700 patients (617 who were treated for a mean duration of 50 weeks) showed that less than 1% (4/717) of NIASPAN-treated patients with normal serum transaminase levels at baseline experienced elevations greater than 3x ULN (one of the four was receiving concomitant HMG-CoA reductase inhibitor therapy).

In the placebo-controlled clinical trials and the long-term extension study, elevations in transaminases did not appear to be related to treatment duration; elevations in AST levels did appear to be dose related. Transaminase elevations were reversible upon discontinuation of NIASPAN.

Liver tests should be performed on all patients during therapy with NIASPAN. Serum transaminase levels, including AST and ALT (SGOT and SGPT), should be monitored before treatment begins, every 6 to 12 weeks for the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3x ULN and are persistent, or if they are associated with symptoms of nausea, fever, and/or malaise, the drug should be discontinued.

***Skeletal Muscle*—**Rare cases of rhabdomyolysis have been associated with concomitant administration of lipid-altering doses (≥1g/day) of niacin and HMG-CoA reductase inhibitors. However, no cases of rhabdomyolysis have been reported in 124 patients who were treated with NIASPAN in combination with various HMG-CoA reductase inhibitors. Physicians contemplating combined therapy with HMG-CoA reductase inhibitors and NIASPAN should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic serum creatine phosphokinase (CPK) and potassium determinations should be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

PRECAUTIONS: *General:* Before instituting therapy with NIASPAN, an attempt should be made to control hyperlipidemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Patients with a past history of jaundice, hepatobiliary disease, or peptic ulcer should be observed closely during NIASPAN therapy. Frequent monitoring of liver function tests and blood glucose should be performed to ascertain that the drug is producing no adverse effects on these organ systems. Diabetic patients may experience a dose-related rise in glucose intolerance, the clinical significance of which is unclear. Diabetic or potentially diabetic patients should be observed closely. Adjustment of diet and/or hypoglycemic therapy may be necessary.

Caution should also be used when NIASPAN is used in patients with unstable angina or in the acute phase of myocardial infarction, particularly when such patients are also receiving vasoactive drugs such as nitrates, calcium channel blockers, or adrenergic blocking agents.

Elevated uric acid levels have occurred with niacin therapy, therefore use with caution in patients predisposed to gout.

NIASPAN has been associated with small but statistically significant dose-related reductions in platelet count (mean of -11% with 2000mg). In addition, NIASPAN has been associated with small but statistically significant increases in prothrombin time (mean of approximately +4%); accordingly, patients undergoing surgery should be carefully evaluated. Caution should be observed when NIASPAN is administered concomitantly with anticoagulants; prothrombin time and platelet counts should be monitored closely in such patients.

In placebo-controlled trials, NIASPAN has been associated with small but statistically significant, dose-related reductions in phosphorus levels (mean of -13% with 2000mg). Although these reductions were transient, phosphorus levels should be monitored periodically in patients at risk for hypophosphatemia.

Niacin is rapidly metabolized by the liver, and excreted through the kidneys. NIASPAN is contraindicated in patients with significant or unexplained hepatic dysfunction (see CONTRAINDICATIONS and WARNINGS) and should be used with caution in patients with renal dysfunction.

Information for Patients: Patients should be advised:—to take NIASPAN at bedtime, after a low-fat snack. Administration on an empty stomach is not recommended;—to carefully follow the prescribed dosing regimen, including the recommended titration schedule, in order to minimize side effects (see DOSAGE AND ADMINISTRATION in full prescribing information);—that flushing is a common side effect of niacin therapy. Flushing may vary in severity, may last for several hours after dosing, and will, by taking NIASPAN at bedtime, most likely occur during sleep; however, if awakened by flushing at night, to get up slowly, especially if feeling dizzy, feeling faint, or taking blood pressure medications;—that taking aspirin (approximately 30 minutes before taking NIASPAN) or a non-steroidal anti-inflammatory drug (e.g., ibuprofen) may minimize flushing;—to avoid ingestion of alcohol or hot drinks around the time of NIASPAN administration, to minimize flushing;—that if NIASPAN therapy is discontinued for an extended length of time, their physician should be contacted prior to re-starting therapy; re-titration is recommended (see DOSAGE AND ADMINISTRATION in full prescribing information; Table 10);—to notify their physician if they are taking vitamins or other nutritional supplements containing niacin or related compounds such as nicotinamide (see Drug Interactions);—to notify their physician if symptoms of dizziness occur;—if diabetic, to notify their physician of changes in blood glucose;—that NIASPAN tablets should not be broken, crushed or chewed, but should be swallowed whole.

Drug Interactions: HMG-CoA Reductase Inhibitors: See **WARNINGS, Skeletal Muscle.**

Antihypertensive Therapy: Niacin may potentiate the effects of ganglionic blocking agents and vasoactive drugs resulting in postural hypotension.

Aspirin: Concomitant aspirin may decrease the metabolic clearance of nicotinic acid. The clinical relevance of this finding is unclear.

Bile Acid Sequestrants: An *in vitro* study was carried out investigating the niacin-binding capacity of colestipol and cholestyramine. About 98% of available niacin was bound to colestipol, with 10 to 30% binding to cholestyramine. These results suggest that 4 to 6 hours, or as great an interval as possible, should elapse between the ingestion of bile acid-binding resins and the administration of NIASPAN.

Other: Concomitant alcohol or hot drinks may increase the side effects of flushing and pruritus and should be avoided around the time of NIASPAN ingestion. Vitamins or other nutritional supplements containing large doses of niacin or related compounds such as nicotinamide may potentiate the adverse effects of NIASPAN.

Drug/Laboratory Test Interactions: Niacin may produce false elevations in some fluorometric determinations of plasma or urinary catecholamines. Niacin may also give false-positive reactions with cupric sulfate solution (Benedict's reagent) in urine glucose tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Niacin administered to mice for a lifetime as a 1% solution in drinking water was not carcinogenic. The mice in this study received approximately 6 to 8 times a human dose of 3000mg/day as determined on a mg/m² basis. Niacin was negative for mutagenicity in the Ames test. No studies on impairment of fertility have been performed. No studies have been conducted with NIASPAN regarding carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy: Pregnancy Category C.: Animal reproduction studies have not been conducted with niacin or with NIASPAN. It is also not known whether niacin at doses typically used for lipid disorders can cause fetal harm when administered to pregnant women or whether it can affect reproductive capacity. If a woman receiving niacin for primary hypercholesterolemia (Types IIa or IIb) becomes pregnant, the drug should be discontinued. If a woman being treated with niacin for hypertriglyceridemia (Types IV or V) conceives, the benefits and risks of continued therapy should be assessed on an individual basis.

Nursing Mothers: Niacin has been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from lipid-altering doses of nicotinic acid, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. No studies have been conducted with NIASPAN in nursing mothers.

Pediatric Use: Safety and effectiveness of niacin therapy in pediatric patients (≤16 years) have not been established. No studies in patients under 21 years-of-age have been conducted with NIASPAN.

ADVERSE REACTIONS: NIASPAN is generally well tolerated; adverse reactions have been mild and transient. In the placebo-controlled clinical trials, flushing episodes (i.e., warmth, redness, itching and/or tingling) were the most common treatment-emergent adverse events (reported by as many as 88% of patients) for NIASPAN. Spontaneous reports suggest that flushing may also be accompanied by symptoms of dizziness, tachycardia, palpitations, shortness of breath, sweating, chills, and/or edema, which in rare cases may lead to syncope. In pivotal studies, fewer than 6% (14/245) of NIASPAN patients discontinued due to flushing. In comparisons of immediate-release (IR) niacin and NIASPAN, although the proportion of patients who flushed was similar, fewer flushing episodes were reported by patients who received NIASPAN. Following 4 weeks of maintenance therapy at daily doses of 1500mg, the incidence of flushing over the 4-week period averaged 8.56 events per patient for IR niacin versus 1.88 following NIASPAN.

Other adverse events occurring in 5% or greater of patients treated with NIASPAN, at least remotely related to NIASPAN, are shown in the table below.

Treatment-Emergent Adverse Events by Dose Level in ≥5% of Patients;
Events Considered At Least Remotely Related to Study Medication

	Placebo-Controlled Studies NIASPAN Treatment†						
			Recommended Daily Maintenance Doses			Greater Than Recommended Daily Doses	
	Placebo (n=157) %	500mg‡ (n=87) %	1000mg (n=110) %	1500mg (n=136) %	2000mg (n=95) %	2500mg‡ (n=49) %	3000mg‡ (n=46) %
Headache	15	5*	9	11	8	4*	4
Pain	3	1	2	5	3	0	2
Pain, Abdominal	3	3	2	3	5	0	0
Diarrhea	8	6	7	6	8	10	11
Dyspepsia	8	2	4	5	5	6	0
Nausea	4	2	5	3	8	10	4
Vomiting	2	0	2	3	6*	8	2
Rhinitis	7	2	5	4	3	0	0
Pruritus	1	6	<1	3	1	0	0
Rash	<1	5	5	4	0	0	0

Note: Percentages are calculated from the total number of patients in each column. AEs are reported at the lowest dose where they occurred.

† Pooled results from placebo-controlled studies; for NIASPAN, n=245 and mean treatment duration = 17 weeks. Number of NIASPAN patients (*n*) are not additive across doses.

‡ The 500mg, 2500mg, and 3000mg/day doses are outside the recommended daily maintenance dosing range; see DOSAGE AND ADMINISTRATION in full prescribing information.

* Significantly different from placebo at p≤0.05; Chi-square test (cell sizes>5), Fisher's Exact test (cell sizes≤5).

In general, the incidence of adverse events was higher in women compared to men.

The following adverse events have also been reported with niacin products, either during clinical trials or in routine patient management.

Body as a Whole: edema, asthenia, chills

Cardiovascular: atrial fibrillation and other cardiac arrhythmias; tachycardia; palpitations; orthostasis; syncope; hypotension

Eye: toxic amblyopia, cystoid macular edema

Gastrointestinal: activation of peptic ulcers and peptic ulceration; jaundice

Metabolic: decreased glucose tolerance; gout

Musculoskeletal: myalgia

Nervous: dizziness, insomnia

Skin: hyper-pigmentation; acanthosis nigricans; maculopapular rash; urticaria; dry skin; sweating

Other: migraine

Clinical Laboratory Abnormalities: Chemistry: Elevations in serum transaminases (see WARNINGS—*Liver Dysfunction*), LDH, fasting glucose, uric acid, total bilirubin, and amylase; reductions in phosphorus

Hematology: Slight reductions in platelet counts and prolongation in prothrombin time (see WARNINGS)

Concomitant Therapy: Preliminary evidence suggests that the lipid-lowering effects of NIASPAN on TC and LDL-C are enhanced with an HMG-CoA reductase inhibitor, e.g., lovastatin, pravastatin, simvastatin, and fluvastatin. Additive effects on LDL-C are also seen when niacin is combined with bile acid-binding resins. (see WARNINGS and PRECAUTIONS, Drug Interactions)

REFERENCES: 1. Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II), *JAMA* 1993;269:3015-3023.

Kos Pharmaceuticals, Inc.
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For more information, visit our website at www.niaspan.com
For more detailed information, please call 1-888-5-NIASPAN or see the full prescribing information.