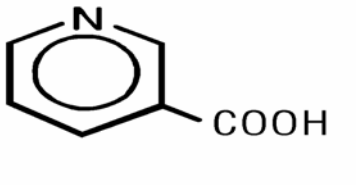
NIASPAN®
niacin extended-release tablets

℞ **ONLY**

DESCRIPTION

NIASPAN® (niacin extended-release tablets), contain niacin, a B-complex vitamin and antihyperlipidemic agent. Niacin (nicotinic acid, or 3-pyridinecarboxylic acid) is a white, crystalline powder, very soluble in water, with the following structural formula:



$C_6H_5NO_2$ M.W. = 123.11

NIASPAN® is an unscored, off-white tablet for oral administration that contains no color additives and is available in three tablet strengths containing 500, 750, and 1000mg niacin. NIASPAN® tablets also contain the inactive ingredients hypromellose, povidone, and stearic acid.

CLINICAL PHARMACOLOGY

Niacin functions in the body after conversion to nicotinamide adenine dinucleotide (NAD) in the NAD coenzyme system. Niacin (but not nicotinamide) in gram doses reduces total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG), and increases high-density lipoprotein cholesterol (HDL-C). The magnitude of individual lipid and lipoprotein responses may be influenced by the severity and type of underlying lipid abnormality. The increase in total HDL-C is associated with an increase in apolipoprotein A-I (Apo A-I) and a shift in the distribution of HDL subfractions. These shifts include an increase in the HDL_2:HDL_3 ratio, and an elevation in lipoprotein A-I (Lp A-I, an HDL particle containing only Apo A-I). Niacin treatment also decreases serum levels of apolipoprotein B-100 (Apo B), the major protein component of the very low-density lipoprotein (VLDL) and LDL fractions, and of Lp(a), a variant form of LDL independently associated with coronary risk.[1] In addition, preliminary reports suggest that niacin causes favorable LDL particle size transformations, although the clinical relevance of this effect requires further investigation. The effect of niacin-induced changes in lipids/lipoproteins on cardiovascular morbidity or mortality in individuals without pre-existing coronary disease has not been

established.

A variety of clinical studies have demonstrated that elevated levels of TC, LDL-C, and Apo B promote human atherosclerosis. Similarly, decreased levels of HDL-C are associated with the development of atherosclerosis. Epidemiological investigations have established that cardiovascular morbidity and mortality vary directly with the level of TC and LDL-C, and inversely with the level of HDL-C.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate-density lipoprotein (IDL), and their remnants, can also promote atherosclerosis. Elevated plasma TG are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease (CHD). As such, total plasma TG have not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Mechanism of Action

The mechanism by which niacin alters lipid profiles has not been well defined. It may involve several actions including partial inhibition of release of free fatty acids from adipose tissue, and increased lipoprotein lipase activity, which may increase the rate of chylomicron triglyceride removal from plasma. Niacin decreases the rate of hepatic synthesis of VLDL and LDL, and does not appear to affect fecal excretion of fats, sterols, or bile acids.

Pharmacokinetics/Metabolism

Absorption

Niacin is rapidly and extensively absorbed (at least 60 to 76% of dose) when administered orally. To maximize bioavailability and reduce the risk of gastrointestinal (GI) upset, administration of NIASPAN® with a low-fat meal or snack is recommended.

Single-dose bioavailability studies have demonstrated that NIASPAN® tablet strengths are not interchangeable.

Distribution

Studies using radiolabeled niacin in mice show that niacin and its metabolites concentrate in the liver, kidney and adipose tissue.

Metabolism

The pharmacokinetic profile of niacin is complicated due to rapid and extensive first-pass metabolism, which is species and dose-rate specific. In humans, one pathway is through a simple conjugation step with glycine to form nicotinuric acid (NUA). NUA is then excreted in the urine, although there may be a small amount of reversible metabolism back to niacin. The other pathway results in the formation of nicotinamide adenine dinucleotide (NAD). It is unclear whether nicotinamide is formed as a precursor to, or

following the synthesis of, NAD. Nicotinamide is further metabolized to at least N-methylnicotinamide (MNA) and nicotinamide-N-oxide (NNO). MNA is further metabolized to two other compounds, N-methyl-2-pyridone-5-carboxamide (2PY) and N-methyl-4-pyridone-5-carboxamide (4PY). The formation of 2PY appears to predominate over 4PY in humans. At the doses used to treat hyperlipidemia, these metabolic pathways are saturable, which explains the nonlinear relationship between niacin dose and plasma concentrations following multiple-dose NIASPAN® administration (Table 1).

Nicotinamide does not have hypolipidemic activity; the activity of the other metabolites is unknown.

Table 1. Mean Steady-State Pharmacokinetic Parameters for Plasma Niacin

NIASPAN®		Niacin	
dose/day	given as	Peak Concentration (µg/mL)	Time to Peak (hrs)
1000mg	2x500mg	0.6	5
1500mg	2x750mg	4.9	4
2000mg	2x1000mg	15.5	5

Elimination

Niacin and its metabolites are rapidly eliminated in the urine. Following single and multiple doses, approximately 60 to 76% of the niacin dose administered as NIASPAN® was recovered in urine as niacin and metabolites; up to 12% was recovered as unchanged niacin after multiple dosing. The ratio of metabolites recovered in the urine was dependent on the dose administered.

Special Populations

Hepatic

No studies have been performed. NIASPAN® should be used with caution in patients with a past history of liver disease, who consume substantial quantities of alcohol, or have unexplained transaminase elevations. NIASPAN® is contraindicated in patients with active liver disease (see **WARNINGS, Liver Dysfunction**).

Renal

There are no data in this population. NIASPAN® should be used with caution in patients with renal disease (see **PRECAUTIONS**).

Gender

Steady-state plasma concentrations of niacin and metabolites after administration of NIASPAN® are generally higher in women than in men, with the magnitude of the difference varying with dose and metabolite. Recovery of niacin and metabolites in urine, however, is generally similar for men and women, indicating that absorption is similar for both genders. The gender differences observed in plasma levels of niacin and its metabolites may be

due to gender-specific differences in metabolic rate or volume of distribution. Data from the clinical trials suggest that women have a greater hypolipidemic response than men at equivalent doses of NIASPAN®.

Niacin Clinical Studies

The role of LDL-C in atherogenesis is supported by pathological observations, clinical studies, and many animal experiments. Observational epidemiological studies have clearly established that high TC or LDL-C and low HDL-C are risk factors for CHD. Additionally, elevated levels of Lp(a) have been shown to be independently associated with CHD risk.[1] The efficacy of niacin in improving lipoprotein lipid profiles, either alone or in combination with other lipid-altering drugs, as an adjunct to diet therapy in the treatment of hyperlipoproteinemia has been well documented.

Niacin's ability to reduce mortality and the risk of definite, nonfatal myocardial infarction (MI) has also been assessed in long-term studies. The Coronary Drug Project,[2] completed in 1975, was designed to assess the safety and efficacy of niacin and other lipid-altering drugs in men 30 to 64 years old with a history of MI. Over an observation period of 5 years, niacin treatment was associated with a statistically significant reduction in nonfatal, recurrent MI. The incidence of definite, nonfatal MI was 8.9% for the 1,119 patients randomized to nicotinic acid versus 12.2% for the 2,789 patients who received placebo (p<0.004). Total mortality was similar in the two groups at 5 years (24.4% with nicotinic acid versus 25.4% with placebo; p=N.S.). At the time of a 15-year follow-up, there were 11% (69) fewer deaths in the niacin group compared to the placebo cohort (52.0% versus 58.2%; p=0.0004).[3] However, mortality at 15 years was not an original endpoint of the Coronary Drug Project. In addition, patients had not received niacin for approximately 9 years, and confounding variables such as concomitant medication use and medical or surgical treatments were not controlled.

The Cholesterol-Lowering Atherosclerosis Study (CLAS) was a randomized, placebo-controlled, angiographic trial testing combined colestipol and niacin therapy in 162 non-smoking males with previous coronary bypass surgery.[4] The primary, per-subject cardiac endpoint was global coronary artery change score. After 2 years, 61% of patients in the placebo cohort showed disease progression by global change score (n=82), compared with only 38.8% of drug-treated subjects (n=80), when both native arteries and grafts were considered (p<0.005); disease regression also occurred more frequently in the drug-treated group (16.2% versus 2.4%; p=0.002). In a follow-up to this trial in a subgroup of 103 patients treated for 4 years, again, significantly fewer patients in the drug-treated group demonstrated progression than in the placebo cohort (48% versus 85%, respectively; p<0.0001).[5]

The Familial Atherosclerosis Treatment Study (FATS) in 146 men ages 62 and younger with Apo B levels ≥125 mg/dL, established coronary artery disease, and family histories of vascular disease, assessed change in severity of disease in the proximal coronary arteries by quantitative arteriography.[6] Patients were given dietary counseling and randomized to treatment with either conventional therapy with double placebo (or placebo plus colestipol if the LDL-C was elevated); lovastatin plus colestipol; or niacin

plus colestipol. In the conventional therapy group, 46% of patients had disease progression (and no regression) in at least one of nine proximal coronary segments; regression was the only change in 11%. In contrast, progression (as the only change) was seen in only 25% in the niacin plus colestipol group, while regression was observed in 39%. Though not an original endpoint of the trial, clinical events (death, MI, or revascularization for worsening angina) occurred in 10 of 52 patients who received conventional therapy, compared with 2 of 48 who received niacin plus colestipol.

The Harvard Atherosclerosis Reversibility Project (HARP) was a randomized placebo-controlled, 2.5-year study of the effect of a stepped-care antihyperlipidemic drug regimen on 91 patients (80 men and 11 women) with CHD and average baseline TC levels less than 250 mg/dL and ratios of TC to HDL-C greater than 4.0.[7] Drug treatment consisted of an HMG-CoA reductase inhibitor administered alone as initial therapy followed by addition of varying dosages of either a slow-release nicotinic acid, cholestyramine, or gemfibrozil. Addition of nicotinic acid to the HMG-CoA reductase inhibitor resulted in further statistically significant mean reductions in TC, LDL-C, and TG, as well as a further increase in HDL-C in a majority of patients (40 of 44 patients). The ratios of TC to HDL-C and LDL-C to HDL-C were also significantly reduced by this combination drug regimen (see **WARNINGS**, ***Skeletal Muscle***).

NIASPAN® Clinical Studies

Placebo-Controlled Clinical Studies in Patients with Primary Hypercholesterolemia and Mixed Dyslipidemia: In two randomized, double-blind, parallel, multi-center, placebo-controlled trials, NIASPAN® dosed at 1000, 1500 or 2000mg daily at bedtime with a low-fat snack for 16 weeks (including 4 weeks of dose escalation) favorably altered lipid profiles compared to placebo (Table 2). Women appeared to have a greater response than men at each NIASPAN® dose level (see *Gender Effect*, below).

Table 2. Lipid Response to NIASPAN® Therapy

Treatment	n	Mean Percent Change from Baseline to Week 16*							
		TC	LDL-C	HDL-C	TC/HDL-C	TG	Lp(a)	Apo B	Apo A-I
NIASPAN® 1000mg qhs	41	-3	-5	+18	-17	-21	-13	-6	+9
NIASPAN® 2000mg qhs	41	-10	-14	+22	-25	-28	-27	-16	+8
Placebo	40	0	-1	+4	-3	0	0	+1	+3
NIASPAN® 1500mg qhs	76	-8	-12	+20	-20	-13	-15	-12	+8
Placebo	73	+2	+1	+2	+1	+12	+2	+1	+2

n = number of patients at baseline;

* Mean percent change from baseline for all NIASPAN® doses was significantly different ($p<0.05$) from placebo for all lipid parameters shown except Apo A-I at 2000mg.

In a double-blind, multi-center, forced dose-escalation study, monthly 500mg

increases in NIASPAN® dose resulted in incremental reductions of approximately 5% in LDL-C and Apo B levels in the daily dose range of 500mg through 2000mg (Table 3). Women again tended to have a greater response to NIASPAN® than men (see *Gender Effect*, below).

Table 3. Lipid Response in Dose-Escalation Study

Treatment	n	Mean Percent Change from Baseline*							
		TC	LDL-C	HDL-C	TC/HDL-C	TG	Lp(a)	Apo B	Apo A-I
Placebo‡	44	-2	-1	+5	-7	-6	-5	-2	+4
NIASPAN®	87								
500mg qhs		-2	-3	+10	-10	-5	-3	-2	+5
1000mg qhs		-5	-9	+15	-17	-11	-12	-7	+8
1500mg qhs		-11	-14	+22	-26	-28	-20	-15	+10
2000mg qhs		-12	-17	+26	-29	-35	-24	-16	+12

n = number of patients enrolled;

‡ Placebo data shown are after 24 weeks of placebo treatment.

* For all NIASPAN® doses except 500mg, mean percent change from baseline was significantly different *(p*<0.05) from placebo for all lipid parameters shown except Lp(a) and Apo A-I which were significantly different from placebo starting with 1500mg and 2000mg, respectively.

Pooled results for major lipids from these three placebo-controlled studies are shown below (Table 4).

Table 4. Selected Lipid Response to NIASPAN® in Placebo-Controlled Clinical Studies*

NIASPAN® Dose	n	Mean Baseline and Median Percent Change from Baseline (25th, 75th Percentiles)		
		LDL-C	HDL-C	TG
1000mg qhs	104			
Baseline (mg/dL)		218	45	172
Percent Change		-7 (-15, 0)	+14 (+7,+23)	-16 (-34,+3)
1500mg qhs	120			
Baseline (mg/dL)		212	46	171
Percent Change		-13 (-21,-4)	+19 (+9,+31)	-25 (-45,-2)
2000mg qhs	85			
Baseline (mg/dL)		220	44	160
Percent Change		-16 (-26,-7)	+22 (+15,+34)	-38 (-52,-14)

*Represents pooled analyses of results; minimum duration on therapy at each dose was 4 weeks.

Gender Effect: Combined data from the three placebo-controlled NIASPAN® studies in patients with primary hypercholesterolemia and mixed dyslipidemia suggest that, at each NIASPAN® dose level studied, changes in lipid concentrations are greater for women than for men (Table 5).

Table 5. Effect of Gender on NIASPAN® Dose Response

NIASPAN® Dose	n	Mean Percent Change from Baseline							
		LDL-C		HDL-C		TG		Apo B	
	(M/F)	M	F	M	F	M	F	M	F
500mg qhs	50/37	-2	-5	+11	+8	-3	-9	-1	-5
1000mg qhs	76/52	-6*	-11*	+14	+20	-10	-20	-5*	-10*
1500mg qhs	104/59	-12	-16	+19	+24	-17	-28	-13	-15
2000mg qhs	75/53	-15	-18	+23	+26	-30	-36	-16	-16

n = number of male/female patients enrolled.

* Percent change significantly different between genders (p<0.05).

Other Patient Populations: In a double-blind, multi-center, 19-week study the lipid-altering effects of NIASPAN® (forced titration to 2000mg qhs) were compared to baseline in patients whose primary lipid abnormality was a low level of HDL-C (HDL-C ≤40 mg/dL, TG ≤400 mg/dL, and LDL-C ≤160, or <130 mg/dL in the presence of CHD). Results are shown below (Table 6).

Table 6. Lipid Response to NIASPAN® in Patients with Low HDL-C

	n	Mean Baseline and Mean Percent Change from Baseline*								
		TC	LDL-C	HDL-C	TC/HDL-C	TG	Lp(a)†	Apo B†	Apo A-I†	Lp A-I††
Baseline (mg/dL)	88	190	120	31	6	194	8	106	105	32
Week 19 (% Change)	71	-3	0	+26	-22	-30	-20	-9	+11	+20

n = number of patients

*Mean percent change from baseline was significantly different (p<0.05) for all lipid parameters shown except LDL-C.

† n=72 at baseline and 69 at week 19.

†† n=30 at baseline and week 19.

At NIASPAN® 2000mg/day, median changes from baseline (25th, 75th percentiles) for LDL-C, HDL-C, and TG were -3% (-14, +12%), +27% (+13, +38%), and -33% (-50, -19%), respectively.

Combination NIASPAN® and Lovastatin Study: In a multi-center, randomized,

double-blind, parallel, 28-week study, a combination tablet of NIASPAN® and lovastatin was compared to each individual component in patients with Type IIa and IIb hyperlipidemia. Using a forced dose-escalation study design, patients received each dose for at least 4 weeks. Patients randomized to treatment with the combination tablet of NIASPAN® and lovastatin initially received 500mg/20mg (expressed as mg of niacin/mg of lovastatin) once daily before bedtime. The dose was increased by 500mg at 4-week intervals (based on the NIASPAN® component) to a maximum dose of 1000mg/20mg in one-half of the patients and 2000mg/40mg in the other half. The NIASPAN® monotherapy group underwent a similar titration from 500mg to 2000mg. The patients randomized to lovastatin monotherapy received 20mg for 12 weeks titrated to 40mg for up to 16 weeks. Up to a third of the patients randomized to the combination tablet of NIASPAN® and lovastatin or NIASPAN® monotherapy discontinued prior to Week 28. Results from this study showed that combination therapy decreased LDL-C, TG and Lp(a), and increased HDL-C in a dose-dependent fashion (Tables 7, 8, 9, and 10). Results from this study for LDL-C mean percent change from baseline (the primary efficacy variable) showed that:

1) LDL-lowering with the combination tablet of NIASPAN® and lovastatin was significantly greater than that achieved with lovastatin 40mg only after 28 weeks of titration to a dose of 2000mg/40mg ($p<0.0001$)

2) The combination tablet of NIASPAN® and lovastatin at doses of 1000mg/20mg or higher achieved greater LDL-lowering than NIASPAN® ($p<0.0001$)

The LDL-C results are summarized in Table 7.

Table 7. LDL-C mean percent change from baseline

Week	Combination tablet of NIASPAN® and lovastatin			NIASPAN®			Lovastatin		
	n*	Dose (mg/mg)	LDL	n*	Dose (mg)	LDL	n*	Dose (mg)	LDL
Baseline	57	-	190.9 mg/dL	61	-	189.7 mg/dL	61	-	185.6 mg/dL
12	47	1000/20	-30%	46	1000	-3%	56	20	-29%
16	45	1000/40	-36%	44	1000	-6%	56	40	-31%
20	42	1500/40	-37%	43	1500	-12%	54	40	-34%
28	42	2000/40	-42%	41	2000	-14%	53	40	-32%

*n = number of patients remaining in trial at each time point

Combination therapy achieved significantly greater HDL-raising compared to lovastatin and NIASPAN® monotherapy at all doses (Table 8).

Table 8. HDL-C mean percent change from baseline

Week	Combination tablet of NIASPAN® and lovastatin			NIASPAN®			Lovastatin		
	n*	Dose (mg/mg)	HDL	n*	Dose (mg)	HDL	n*	Dose (mg)	HDL
Baseline	57	-	45 mg/dL	61	-	47 mg/dL	61	-	43 mg/dL
12	47	1000/20	+20%	46	1000	+14%	56	20	+3%
16	45	1000/40	+20%	44	1000	+15%	56	40	+5%
20	42	1500/40	+27%	43	1500	+22%	54	40	+6%
28	42	2000/40	+30%	41	2000	+24%	53	40	+6%

*n = number of patients remaining in trial at each time point

In addition, combination therapy achieved significantly greater TG-lowering at doses of 1000mg/20mg or greater compared to lovastatin and NIASPAN® monotherapy (Table 9).

Table 9. TG median percent change from baseline

Week	Combination tablet of NIASPAN® and lovastatin			NIASPAN®			Lovastatin		
	n*	Dose (mg/mg)	TG	n*	Dose (mg)	TG	n*	Dose (mg)	TG
Baseline	57	-	174 mg/dL	61	-	186 mg/dL	61	-	171 mg/dL
12	47	1000/20	-32%	46	1000	-22%	56	20	-20%
16	45	1000/40	-39%	44	1000	-23%	56	40	-17%
20	42	1500/40	-44%	43	1500	-31%	54	40	-21%
28	42	2000/40	-44%	41	2000	-31%	53	40	-20%

*n = number of patients remaining in trial at each time point

The Lp(a)-lowering effects of combination therapy and NIASPAN® monotherapy were similar, and both were superior to lovastatin (Table 10). The independent effect of lowering Lp(a) with NIASPAN® or combination therapy on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Table 10. Lp(a) median percent change from baseline

Week	Combination tablet of NIASPAN® and lovastatin			NIASPAN®			Lovastatin		
	n*	Dose (mg/mg)	Lp(a)	n*	Dose (mg)	Lp(a)	n*	Dose (mg)	Lp(a)
Baseline	57	-	34 mg/dL	61	-	41 mg/dL	60	-	42 mg/dL
12	47	1000/20	-9%	46	1000	-8%	55	20	+8%
16	45	1000/40	-9%	44	1000	-12%	55	40	+8%
20	42	1500/40	-17%	43	1500	-22%	53	40	+6%
28	42	2000/40	-22%	41	2000	-32%	52	40	0%

*n = number of patients remaining in trial at each time point

INDICATIONS AND USAGE

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. 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;[8] Table 11). Prior to initiating therapy with niacin, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile obtained to measure TC, HDL-C, and TG.

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; Table 12), when the response to an appropriate diet has been inadequate.

2. NIASPAN® in combination with lovastatin is indicated for the treatment of primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson Types IIa and IIb; Table 12) in:

   - Patients treated with lovastatin who require further TG-lowering or HDL-raising who may benefit from having niacin added to their regimen
   - Patients treated with niacin who require further LDL-lowering who may benefit from having lovastatin added to their regimen

Combination therapy is not indicated as initial therapy. (See **DOSAGE AND ADMINISTRATION**.)

3. In patients with a history of myocardial infarction and hypercholesterolemia, niacin is indicated to reduce the risk of recurrent nonfatal myocardial infarction.

4. 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.

5. 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; Table 12), when the response to an appropriate diet, or diet plus monotherapy, has been inadequate.

6. Niacin is also indicated as adjunctive therapy for treatment of adult patients with very high serum triglyceride levels (Types IV and V hyperlipidemia; Table 12) who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them. Such patients typically have serum TG levels over 2000 mg/dL and have elevations of VLDL-C as well as fasting chylomicrons (Type V hyperlipidemia; Table 12). Patients who consistently have total serum or plasma TG below 1000 mg/dL are unlikely to develop pancreatitis. Therapy with niacin may be considered for those patients with TG elevations between 1000 and 2000 mg/dL who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis. Some Type IV patients with TG under 1000 mg/dL may, through dietary or alcohol indiscretion, convert to a Type V pattern with massive TG elevations accompanying fasting chylomicronemia, but the influence of niacin therapy on risk of pancreatitis in such situations has not been adequately studied. Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma TG, but who have normal levels of VLDL-C. Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV, and V hyperlipoproteinemia.[9]

Table 11. NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD† or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional) ††
2+ Risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk factor†††	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

† CHD, coronary heart disease

†† Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

††† Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dL, non-HDL-C (TC minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

Table 12. Classification of Hyperlipoproteinemias

Type	Lipoproteins Elevated	Lipid Elevations	
		Major	Minor
I (rare)	chylomicrons	TG	↑→TC
IIa	LDL	TC	—
IIb	LDL, VLDL	TC	TG
III (rare)	IDL	TC/TG	—
IV	VLDL	TG	↑→TC
V (rare)	chylomicrons, VLDL	TG	↑→TC

TC = total cholesterol; TG = triglycerides; LDL = low-density lipoprotein;

VLDL = very low-density lipoprotein; IDL = intermediate-density lipoprotein

↑→ = increased or no change

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., 500mg qhs) and the NIASPAN® dose should then be titrated to the desired therapeutic response (see DOSAGE AND ADMINISTRATION).

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 (ULN) during treatment with NIASPAN®. In these studies, fewer than 1% (2/245) of NIASPAN® patients discontinued due to transaminase elevations greater than 2 times the ULN.

In three safety and efficacy studies with a combination tablet of NIASPAN® and lovastatin involving titration to final daily doses (expressed as mg of niacin/ mg of lovastatin) 500mg/10mg to 2500mg/40mg, ten of 1028 patients (1.0%) experienced reversible elevations in AST/ALT to more than 3 times the upper limit of normal (ULN). Three of ten elevations occurred at doses outside the recommended dosing limit of 2000mg/40mg; no patient receiving 1000mg/20mg had 3-fold elevations in AST/ALT.

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 3 times 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 (≥1 g/day) of niacin and HMG-CoA reductase inhibitors. In clinical studies with a combination tablet of NIASPAN® and lovastatin, no cases of rhabdomyolysis and one suspected case of myopathy have been reported in 1079 patients who were treated with doses up to 2000mg of NIASPAN® and 40mg of lovastatin daily for periods up to 2 years. **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 an MI, 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**);
- that flushing is a common side effect of niacin therapy that usually subsides after several weeks of consistent niacin use. 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 nonsteroidal 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**; Table 14);
- 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 3000 mg/day as determined on a mg/m^2 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®.

Geriatric Use

Of 979 patients in clinical studies of NIASPAN®, 21% of the patients were age 65 and over. No overall differences in safety and effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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 Table 13 below.

Table 13. 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) %	3000 mg‡ (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	8*	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**.

* Significantly different from placebo at $p \leq 0.05$; 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 NIASPAN® or other niacin products, either during clinical trials or in routine patient management.

Body as a Whole: generalized edema; face edema; peripheral 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; eructation; flatulence

Metabolic: decreased glucose tolerance; gout

Musculoskeletal:	myalgia; myasthenia
Nervous:	dizziness; insomnia; leg cramps; nervousness; paresthesia
Respiratory:	dyspnea
Skin:	hyper-pigmentation; acanthosis nigricans; maculopapular rash; urticaria; dry skin; sweating
Other:	migraine

Hypersensitivity reactions: An apparent hypersensitivity reaction has been reported rarely that has included one or more of the following features: anaphylaxis, angioedema, urticaria, flushing, dyspnea, tongue edema, larynx edema, face edema, peripheral edema, laryngismus, and vesiculobullous rash.

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**)

DRUG ABUSE AND DEPENDENCE

Niacin is a non-narcotic drug. It has no known addiction potential in humans.

OVERDOSAGE

Supportive measures should be undertaken in the event of an overdose.

DOSAGE AND ADMINISTRATION

NIASPAN® should be taken at bedtime, after a low-fat snack, and doses should be individualized according to patient response. Therapy with NIASPAN® must be initiated at 500mg qhs in order to reduce the incidence and severity of side effects which may occur during early therapy. The recommended dose escalation is shown in Table 14 below.

Table 14. Recommended Dosing

	Week(s)	Daily dose	NIASPAN® Dosage
INITIAL TITRATION SCHEDULE	1 to 4	500mg	1 NIASPAN® 500mg tablet at bedtime
	5 to 8	1000mg	2 NIASPAN® 500mg tablets at bedtime
	*	1500mg	2 NIASPAN® 750mg tablets or 3 NIASPAN® 500mg tablets at bedtime
	*	2000mg	2 NIASPAN® 1000mg tablets or 4 NIASPAN® 500mg tablets at bedtime

* After Week 8, titrate to patient response and tolerance. If response to 1000mg daily is inadequate, increase dose to 1500mg daily; may subsequently increase dose to 2000mg daily. Daily dose should not be increased more than 500mg in a 4-week period, and doses above 2000mg daily are not recommended. Women may respond at lower doses than men.

Maintenance Dose:

The daily dosage of NIASPAN® should not be increased by more than 500mg in any 4-week period. The recommended maintenance dose is 1000mg (two 500mg tablets) to 2000mg (two 1000mg tablets or four 500mg tablets) once daily at bedtime. Doses greater than 2000mg daily are not recommended. Women may respond at lower NIASPAN® doses than men (see **CLINICAL PHARMACOLOGY**, *Gender Effect*).

If lipid response to NIASPAN® alone is insufficient (see NCEP treatment guidelines; Table 11), or if higher doses of NIASPAN® are not well tolerated, some patients may benefit from combination therapy with a bile acid binding resin or an HMG-CoA reductase inhibitor. (See **WARNINGS, PRECAUTIONS, Drug Interactions, Concomitant Therapy** below, and **CLINICAL PHARMACOLOGY, NIASPAN® Clinical Studies**).

Flushing of the skin (see **ADVERSE REACTIONS**) may be reduced in frequency or severity by pretreatment with aspirin (taken 30 minutes prior to NIASPAN® dose) or non-steroidal anti-inflammatory drugs. Tolerance to this flushing develops rapidly over the course of several weeks. Flushing, pruritus, and gastrointestinal distress are also greatly reduced by slowly increasing the dose of niacin and avoiding administration on an empty stomach.

Equivalent doses of NIASPAN® should **not** be substituted for sustained-release (modified-release, timed-release) niacin preparations or immediate-release (crystalline) niacin (see **WARNINGS**). Patients previously receiving

other niacin products should be started with the recommended NIASPAN® titration schedule (see Table 14), and the dose should subsequently be individualized based on patient response. Single-dose bioavailability studies have demonstrated that NIASPAN® tablet strengths are not interchangeable.

If NIASPAN® therapy is discontinued for an extended period, reinstitution of therapy should include a titration phase (see Table 14).

NIASPAN® tablets should be taken whole and should not be broken, crushed or chewed before swallowing.

Concomitant Therapy

Concomitant Therapy with Lovastatin

Patients already receiving a stable dose of lovastatin who require further TG-lowering or HDL-raising (e.g., to achieve NCEP non-HDL-C goals), may receive concomitant dosage titration with NIASPAN® per NIASPAN® recommended initial titration schedule (see Table 14, **DOSAGE AND ADMINISTRATION** section). For patients already receiving a stable dose of NIASPAN® who require further LDL-lowering (e.g., to achieve NCEP LDL-C goals; Table 11), the usual recommended starting dose of lovastatin is 20mg once a day. Dose adjustments should be made at intervals of 4 weeks or more. Combination therapy with NIASPAN® and lovastatin should not exceed doses of 2000mg and 40mg daily, respectively.

Dosage in Patients with Renal or Hepatic Insufficiency

Use of NIASPAN® in patients with renal or hepatic insufficiency has not been studied. NIASPAN® is contraindicated in patients with significant or unexplained hepatic dysfunction. NIASPAN® should be used with caution in patients with renal insufficiency (see **WARNINGS, PRECAUTIONS**).

HOW SUPPLIED

NIASPAN® is supplied as unscored, off-white capsule-shaped tablets containing 500, 750 or 1000mg of niacin in an extended-release formulation. Tablets are debossed KOS on one side and the tablet strength (500, 750 or 1000) on the other side. Tablets are supplied in bottles of 100 as shown below.

500mg tablets: bottles of 100 - NDC# 60598-001-01

750mg tablets: bottles of 100 - NDC# 60598-002-01

1000mg tablets: bottles of 100 - NDC# 60598-003-01

Store at room temperature (20 to 25°C or 68 to 77°F).

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