

DN2011V1-proposed-niaspan-2009-sep-22

1 of 38

## NIASPAN - niacin tablet, film coated, extended release

### Abbott Laboratories

#### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NIASPAN<sup>®</sup> safely and effectively. See full prescribing information for NIASPAN.

NIASPAN (niacin extended-release) tablet, film coated, extended release for oral use.

Initial U.S. Approval: 1997

#### INDICATIONS AND USAGE

NIASPAN contains extended-release niacin (nicotinic acid), and is indicated:

- To reduce elevated TC, LDL-C, Apo B and TG, and to increase HDL-C in patients with primary hyperlipidemia and mixed dyslipidemia.(1)
- *In combination with simvastatin or lovastatin:* to treat primary hyperlipidemia and mixed dyslipidemia when treatment with NIASPAN, simvastatin, or lovastatin monotherapy is considered inadequate.(1)
- To reduce the risk of recurrent nonfatal myocardial infarction in patients with a history of myocardial infarction and hyperlipidemia.(1)
- *In combination with a bile acid binding resin:*
  - Slows progression or promotes regression of atherosclerotic disease in patients with a history of coronary artery disease (CAD) and hyperlipidemia. (1)
  - As an adjunct to diet to reduce elevated TC and LDL-C in adult patients with primary hyperlipidemia. (1)
- To reduce TG in adult patients with severe hypertriglyceridemia.(1)

Limitations of use:

No incremental benefit of NIASPAN coadministered with simvastatin or lovastatin on cardiovascular morbidity and mortality over and above that demonstrated for niacin, simvastatin and lovastatin monotherapy, has been established.

NIASPAN has not been studied in Fredrickson Type I and III dyslipidemias.

#### DOSAGE AND ADMINISTRATION

- NIASPAN should be taken at bedtime with a low-fat snack. (2)
- Dose range: 500 mg to 2000 mg once daily. (2)
- Therapy with NIASPAN must be initiated at 500 mg at bedtime in order to reduce the incidence and severity of side effects which may occur during early therapy and should not be increased by more than 500 mg in any four week period. (2)
- Maintenance dose: 1000 to 2000 mg once daily. (2)
- Doses greater than 2000 mg daily are not recommended. (2)
- Concomitant therapy with lovastatin: Initial dose of lovastatin is 20 mg once a day; combination therapy with NIASPAN and lovastatin should not exceed doses of 2000 mg and 40 mg daily, respectively. (2)
- Concomitant therapy with simvastatin: Initial dose of simvastatin is 20 mg once a day; combination therapy with NIASPAN and simvastatin should not exceed doses of 2000 mg and 40 mg daily, respectively. (2)

#### DOSAGE FORMS AND STRENGTHS

Unscored film-coated tablets for oral administration: 500, 750 and 1000 mg niacin extended-release. (3)

#### CONTRAINDICATIONS

- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels. (4, 5.2)
- Active peptic ulcer disease. (4)
- Arterial bleeding. (4)
- Known hypersensitivity to product components. (4, 6.1)

#### WARNINGS AND PRECAUTIONS

- Severe hepatic toxicity has occurred in patients substituting sustained-release niacin for immediate-release niacin at equivalent doses. (5.2)
- Myopathy has been reported in patients taking NIASPAN. The risk for myopathy and rhabdomyolysis are increased when lovastatin or simvastatin are coadministered with NIASPAN, particularly in elderly patients and patients with diabetes, renal failure, or uncontrolled hypothyroidism. (5.1)
- Liver enzyme abnormalities and monitoring: Persistent elevations in hepatic transaminase can occur. Monitor liver enzymes before and during treatment. (5.2)
- Use with caution in patients with unstable angina or in the acute phase of an MI. (5)
- NIASPAN can increase serum glucose levels. Glucose levels should be closely monitored in diabetic or potentially diabetic patients particularly during the first few months of use or dose adjustment. (5.3)

DN2011V1-proposed-niaspan-2009-sep-22

2 of 38

#### ADVERSE REACTIONS

Most common adverse reactions (incidence >5% and greater than placebo) are flushing, diarrhea, nausea, vomiting, increased cough, and pruritus.(6.1)

Flushing of the skin may be reduced in frequency or severity by pretreatment with aspirin (up to the recommended dose of 325 mg taken 30 minutes prior to NIASPAN dose).(2)

To report SUSPECTED ADVERSE REACTIONS, contact Abbott Laboratories at 1-800-633-9110 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- Statins: Caution should be used when prescribing niacin with statins as these agents can increase risk of myopathy/rhabdomyolysis.(5.1,7.1)
- Bile Acid Sequestrants: Bile acid sequestrants have a high niacin-binding capacity and should be taken at least 4 - 6 hours before NIASPAN administration. (7.2)

#### USE IN SPECIFIC POPULATIONS

- Renal impairment: NIASPAN should be used with caution in patients with renal impairment. (5, 8.6)
- Hepatic impairment: NIASPAN is contraindicated in active liver disease or significant or unexplained hepatic dysfunction or unexplained elevations of serum transaminases. (4,5, 5.2, 8.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 09/2009

---

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1 INDICATIONS AND USAGE

### 2 DOSAGE AND ADMINISTRATION

### 3 DOSAGE FORMS AND STRENGTHS

### 4 CONTRAINDICATIONS

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Skeletal Muscle

#### 5.2 Liver Dysfunction

#### 5.3 Laboratory Abnormalities

### 6 ADVERSE REACTIONS

#### 6.1 Clinical Studies Experience

#### 6.2 Postmarketing Experience

### 7 DRUG INTERACTIONS

#### 7.1 Statins

#### 7.2 Bile Acid Sequestrants

#### 7.3 Aspirin

#### 7.4 Antihypertensive Therapy

#### 7.5 Other

#### 7.6 Laboratory Test Interactions

## **8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment
- 8.8 Gender

## **10 OVERDOSAGE**

## **11 DESCRIPTION**

## **12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

## **13 NONCLINICAL TOXICOLOGY**

- 13.1 Carcinogenesis and Mutagenesis and Impairment of Fertility

## **14 CLINICAL STUDIES**

- 14.1 Niacin Clinical Studies
- 14.2 NIASPAN Clinical Studies
- 14.3 NIASPAN and Lovastatin Clinical Studies
- 14.4 NIASPAN and Simvastatin Clinical Studies

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

## **17 PATIENT COUNSELING INFORMATION**

- 17.1 Patient Counseling

\* Sections or subsections omitted from the full prescribing information are not listed

---

## **FULL PRESCRIBING INFORMATION**

### **1 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 hyperlipidemia.

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.

1. NIASPAN is indicated to reduce elevated TC, LDL-C, Apo B and TG levels, and to increase HDL-C in patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb).
2. NIASPAN in combination with simvastatin or lovastatin is indicated for the treatment of primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb) when treatment with NIASPAN, simvastatin, or lovastatin monotherapy is considered inadequate.
3. In patients with a history of myocardial infarction and hyperlipidemia, niacin is indicated to reduce the risk of recurrent nonfatal myocardial infarction.
4. In patients with a history of coronary artery disease (CAD) and hyperlipidemia, 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 to reduce elevated TC and LDL-C levels in adult patients with primary hyperlipidemia (Type IIa).
6. Niacin is also indicated as adjunctive therapy for treatment of adult patients with severe hypertriglyceridemia (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.

### Limitations of Use

No incremental benefit of NIASPAN coadministered with simvastatin or lovastatin on cardiovascular morbidity and mortality over and above that demonstrated for niacin, simvastatin, or lovastatin monotherapy has been established. NIASPAN has not been studied in Fredrickson Type I and III dyslipidemias.

### 2 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 500 mg at bedtime 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 1](#) below.

**Table 1. Recommended Dosing**

---

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

\* After Week 8, titrate to patient response and tolerance. If response to 1000 mg daily is inadequate, increase dose to 1500 mg daily; may subsequently increase dose to 2000 mg daily. Daily dose should not be increased more than 500 mg in a 4-week period, and doses above 2000 mg 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 500 mg in any 4–week period. The recommended maintenance dose is 1000 mg (two 500 mg tablets or one 1000 mg tablet) to 2000 mg (two 1000 mg tablets or four 500 mg tablets) once daily at bedtime. Doses greater than 2000 mg daily are not recommended. Women may respond at lower NIASPAN doses than men [see *Clinical Studies (14.2)*].

Single-dose bioavailability studies have demonstrated that two of the 500 mg and one of the 1000 mg tablet strengths are interchangeable but three of the 500 mg and two of the 750 mg tablet strengths are not interchangeable.

If lipid response to NIASPAN alone is insufficient or if higher doses of NIASPAN are not well tolerated, some patients may benefit from combination therapy with a bile acid binding resin or statin [see *Drug Interactions (7.3)*, *Concomitant Therapy* below and *Clinical Studies (14.3, 14.4)*].

DN2011V1-proposed-niaspan-2009-sep-22

6 of 38

Flushing of the skin [*see Adverse Reactions (6.1)*] may be reduced in frequency or severity by pretreatment with aspirin (up to the recommended dose of 325 mg taken 30 minutes prior to NIASPAN dose). 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. Concomitant alcoholic, hot drinks or spicy foods may increase the side effects of flushing and pruritus and should be avoided around the time of NIASPAN ingestion.

Equivalent doses of NIASPAN should not be substituted for sustained-release (modified-release, timed-release) niacin preparations or immediate-release (crystalline) niacin [*see Warnings and Precautions (5)*]. Patients previously receiving other niacin products should be started with the recommended NIASPAN titration schedule (see [Table 1](#)), and the dose should subsequently be individualized based on patient response.

If NIASPAN therapy is discontinued for an extended period, reinstatement of therapy should include a titration phase (see [Table 1](#)).

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

### Concomitant Therapy

#### *Concomitant Therapy with Lovastatin or Simvastatin*

Patients already receiving a stable dose of lovastatin or simvastatin 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 Dosage and Administration (2)*]. For patients already receiving a stable dose of NIASPAN who require further LDL-lowering (e.g., to achieve NCEP LDL-C goals), the usual recommended starting dose of lovastatin and simvastatin is 20 mg once a day. Dose adjustments should be made at intervals of 4 weeks or more. Combination therapy with NIASPAN and lovastatin or NIASPAN and simvastatin should not exceed doses of 2000 mg NIASPAN and 40 mg lovastatin or simvastatin daily.

#### *Dosage in Patients with Renal or Hepatic Impairment*

Use of NIASPAN in patients with renal or hepatic impairment 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 impairment [*see Warnings and Precautions (5)*].

DN2011V1-proposed-niaspan-2009-sep-22

7 of 38

### 3 DOSAGE FORMS AND STRENGTHS

- 500 mg unscored, medium-orange, film-coated, capsule-shaped tablets
- 750 mg unscored, medium-orange, film-coated, capsule-shaped tablets
- 1000 mg unscored, medium-orange, film-coated, capsule-shaped tablets

### 4 CONTRAINDICATIONS

NIASPAN is contraindicated in the following conditions:

- Active liver disease or unexplained persistent elevations in hepatic transaminases [*see Warnings and Precautions (5.2)*]
- Patients with active peptic ulcer disease
- Patients with arterial bleeding
- Hypersensitivity to niacin or any component of this medication [*see Adverse Reactions (6.1)*]

### 5 WARNINGS AND PRECAUTIONS

**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 at bedtime) and the NIASPAN dose should then be titrated to the desired therapeutic response [*see Dosage and Administration (2)*].**

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.

Niacin is rapidly metabolized by the liver, and excreted through the kidneys. NIASPAN is contraindicated in patients with significant or unexplained hepatic impairment [*see Contraindications (4) and Warnings and Precautions (5.2)*] and should be used with caution in patients with renal impairment. Patients with a past history of jaundice, hepatobiliary disease, or peptic ulcer should be observed closely during NIASPAN therapy.

#### 5.1 Skeletal Muscle

Cases of rhabdomyolysis have been associated with concomitant administration of lipid-altering doses ( $\geq 1$  g/day) of niacin and statins. Physicians contemplating combined therapy with statins 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

DN2011V1-proposed-niaspan-2009-sep-22

8 of 38

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.

The risk for myopathy and rhabdomyolysis are increased when lovastatin or simvastatin are coadministered with NIASPAN, particularly in elderly patients and patients with diabetes, renal failure, or uncontrolled hypothyroidism.

## 5.2 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 have been associated with abnormal liver tests. In three placebo-controlled clinical trials involving titration to final daily NIASPAN doses ranging from 500 to 3000 mg, 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) 500 mg/10 mg to 2500 mg/40 mg, ten of 1028 patients (1.0%) experienced reversible elevations in AST/ALT to more than 3 times the ULN. Three of ten elevations occurred at doses outside the recommended dosing limit of 2000 mg/40 mg; no patient receiving 1000 mg/20 mg had 3-fold elevations in AST/ALT.

Niacin extended-release and simvastatin can cause abnormal liver tests. In a simvastatin-controlled, 24 week study with a fixed dose combination of NIASPAN and simvastatin in 641 patients, there were no persistent increases (more than 3x the ULN) in serum transaminases. In three placebo-controlled clinical studies of extended-release niacin there were no patients with normal serum transaminase levels at baseline who experienced elevations to more than 3x the ULN. Persistent increases (more than 3x the ULN) in serum transaminases have occurred in approximately 1% of patients who

DN2011V1-proposed-niaspan-2009-sep-22

9 of 38

received simvastatin in clinical studies. When drug treatment was interrupted or discontinued in these patients, the transaminases levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

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 function 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.

### 5.3 Laboratory Abnormalities

*Increase in Blood Glucose:* Niacin treatment can increase fasting blood glucose. Frequent monitoring of blood glucose should be performed to ascertain that the drug is producing no adverse effects. Diabetic patients may experience a dose-related increase in glucose intolerance. Diabetic or potentially diabetic patients should be observed closely during treatment with NIASPAN, particularly during the first few months of use or dose adjustment; adjustment of diet and/or hypoglycemic therapy may be necessary.

*Reduction in platelet count:* NIASPAN has been associated with small but statistically significant dose-related reductions in platelet count (mean of -11% with 2000 mg). Caution should be observed when NIASPAN is administered concomitantly with anticoagulants; platelet counts should be monitored closely in such patients.

*Increase in Prothrombin Time (PT):* 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 should be monitored closely in such patients.

DN2011V1-proposed-niaspan-2009-sep-22

10 of 38

*Increase in Uric Acid:* Elevated uric acid levels have occurred with niacin therapy, therefore use with caution in patients predisposed to gout.

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

## 6 ADVERSE REACTIONS

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

### 6.1 Clinical Studies Experience

In the placebo-controlled clinical trials database of 402 patients (age range 21-75 years, 33% women, 89% Caucasians, 7% Blacks, 3% Hispanics, 1% Asians) with a median treatment duration of 16 weeks, 16% of patients on NIASPAN and 4% of patients on placebo discontinued due to adverse reactions. The most common adverse reactions in the group of patients treated with NIASPAN that led to treatment discontinuation and occurred at a rate greater than placebo were flushing (6% vs. 0%), rash (2% vs. 0%), diarrhea (2% vs. 0%), nausea (1% vs. 0%), and vomiting (1% vs. 0%). The most commonly reported adverse reactions (incidence >5% and greater than placebo) in the NIASPAN controlled clinical trial database of 402 patients were flushing, diarrhea, nausea, vomiting, increased cough and pruritus.

In the placebo-controlled clinical trials, flushing episodes (i.e., warmth, redness, itching and/or tingling) were the most common treatment-emergent adverse reactions (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, burning sensation/skin burning sensation, chills, and/or edema, which in rare cases may lead to syncope. In pivotal studies, 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 1500 mg, the incidence of flushing over the 4-week period averaged 8.6 events per patient for IR niacin versus 1.9 following NIASPAN.

DN2011V1-proposed-niaspan-2009-sep-22

11 of 38

Other adverse reactions occurring in  $\geq 5\%$  of patients treated with NIASPAN and at an incidence greater than placebo are shown in [Table 2](#) below.

**Table 2. Treatment-Emergent Adverse Reactions by Dose Level in  $\geq 5\%$  of Patients and at an Incidence Greater than Placebo; Regardless of Causality Assessment in Placebo-Controlled Clinical Trials**

	Placebo-Controlled Studies				
	NIASPAN Treatment@				
	Recommended Daily Maintenance Doses †				
	Placebo (n = 157)	500 mg‡ (n = 87)	1000 mg (n = 110)	1500 mg (n = 136)	2000 mg (n = 95)
	%	%	%	%	%
<b>Gastrointestinal Disorders</b>					
Diarrhea	13	7	10	10	14
Nausea	7	5	6	4	11
Vomiting	4	0	2	4	9
<b>Respiratory</b>					
Cough, Increased	6	3	2	< 2	8
<b>Skin and Subcutaneous Tissue Disorders</b>					
Pruritus	2	8	0	3	0
Rash	0	5	5	5	0
<b>Vascular Disorders</b>					
Flushing&	19	68	69	63	55

Note: Percentages are calculated from the total number of patients in each column.

† Adverse reactions are reported at the initial dose where they occur.

@ Pooled results from placebo-controlled studies; for NIASPAN, n = 245 and median treatment duration = 16 weeks. Number of NIASPAN patients (n) are not additive across doses.

‡ The 500 mg/day dose is outside the recommended daily maintenance dosing range

[see *Dosage and Administration (2)*].

& 10 patients discontinued before receiving 500 mg, therefore they were not included.

DN2011V1-proposed-niaspan-2009-sep-22

13 of 38

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

## 6.2 Postmarketing Experience

Because the below reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following additional adverse reactions have been identified during post-approval use of NIASPAN:

Hypersensitivity reactions, including anaphylaxis, angioedema, urticaria, flushing, dyspnea, tongue edema, larynx edema, face edema, peripheral edema, laryngismus, and vesiculobullous rash; maculopapular rash; dry skin; tachycardia; palpitations; atrial fibrillation; other cardiac arrhythmias; syncope; hypotension; postural hypotension; blurred vision; macular edema; peptic ulcers; eructation; flatulence; hepatitis; jaundice; decreased glucose tolerance; gout; myalgia; myopathy; dizziness; insomnia; asthenia; nervousness; paresthesia; dyspnea; sweating; burning sensation/skin burning sensation; skin discoloration, and migraine.

### *Clinical Laboratory Abnormalities*

Chemistry: Elevations in serum transaminases [*see Warnings and Precautions (5.2)*], LDH, fasting glucose, uric acid, total bilirubin, amylase and creatine kinase, and reduction in phosphorus.

Hematology: Slight reductions in platelet counts and prolongation in prothrombin time [*see Warnings and Precautions (5.3)*].

## 7 DRUG INTERACTIONS

### 7.1 Statins

Caution should be used when prescribing niacin ( $\geq 1$  gm/day) with statins as these drugs can increase risk of myopathy/rhabdomyolysis. Combination therapy with NIASPAN and lovastatin or NIASPAN and simvastatin should not exceed doses of 2000 mg NIASPAN and 40 mg lovastatin or simvastatin daily. [*see Warnings and Precautions (5) and Clinical Pharmacology (12.3)*].

### 7.2 Bile Acid Sequestrants

DN2011V1-proposed-niaspan-2009-sep-22

14 of 38

An *in vitro* study results suggest that the bile acid-binding resins have high niacin binding capacity. Therefore, 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 [see *Clinical Pharmacology (12.3)*].

### 7.3 Aspirin

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

### 7.4 Antihypertensive Therapy

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

### 7.5 Other

Vitamins or other nutritional supplements containing large doses of niacin or related compounds such as nicotinamide may potentiate the adverse effects of NIASPAN.

### 7.6 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.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 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 hyperlipidemia (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.

All statins are contraindicated in pregnant and nursing women. When NIASPAN is administered with a statin in a woman of childbearing potential, refer to the pregnancy category and product labeling for the statin.

DN2011V1-proposed-niaspan-2009-sep-22

15 of 38

### 8.3 Nursing Mothers

Niacin is excreted into human milk but the actual infant dose or infant dose as a percent of the maternal dose is not known. 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.

### 8.4 Pediatric Use

Safety and effectiveness of niacin therapy in pediatric patients ( $\leq 16$  years) have not been established.

### 8.5 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.

### 8.6 Renal Impairment

No studies have been performed in this population. NIASPAN should be used with caution in patients with renal impairment [*see Warnings and Precautions (5)*].

### 8.7 Hepatic Impairment

No studies have been performed in this population. NIASPAN should be used with caution in patients with a past history of liver disease and/or who consume substantial quantities of alcohol. Active liver disease, unexplained transaminase elevations and significant or unexplained hepatic dysfunction are contraindications to the use of NIASPAN [*see Contraindications (4.0) and Warnings and Precautions (5.2)*].

### 8.8 Gender

Data from the clinical trials suggest that women have a greater hypolipidemic response than men at equivalent doses of NIASPAN.

## 10 OVERDOSAGE

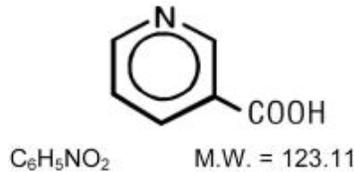
Supportive measures should be undertaken in the event of an overdose.

## 11 DESCRIPTION

DN2011V1-proposed-niaspan-2009-sep-22

16 of 38

NIASPAN (niacin tablet, film-coated extended-release), contains niacin, which at therapeutic doses is an antihyperlipidemic agent. Niacin (nicotinic acid, or 3-pyridinecarboxylic acid) is a white, crystalline powder, very soluble in water, with the following structural formula:



NIASPAN is an unscored, medium-orange, film-coated tablet for oral administration and is available in three tablet strengths containing 500, 750, and 1000 mg niacin. NIASPAN tablets also contain the inactive ingredients hypromellose, povidone, stearic acid, and polyethylene glycol, and the following coloring agents: FD&C yellow #6/sunset yellow FCF Aluminum Lake, synthetic red and yellow iron oxides, and titanium dioxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 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.

### 12.2 Pharmacodynamics

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 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<sub>2</sub>:HDL<sub>3</sub> ratio, and an elevation in lipoprotein A-I (Lp A-I, an HDL-C 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. In addition, preliminary reports suggest that niacin causes favorable LDL particle size transformations, although

DN2011V1-proposed-niaspan-2009-sep-22

17 of 38

the clinical relevance of this effect requires further investigation. The effect of niacin-induced changes in lipids/proteins on cardiovascular morbidity or mortality in individuals without preexisting 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 Total-C 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 has 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.

### 12.3 Pharmacokinetics

#### *Absorption*

Due to extensive and saturable first-pass metabolism, niacin concentrations in the general circulation are dose dependent and highly variable. Time to reach the maximum niacin plasma concentrations was about 5 hours following NIASPAN. To 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 the 500 mg and 1000 mg tablet strengths are dosage form equivalent but the 500 mg and 750 mg tablet strengths are not dosage form equivalent.

#### *Metabolism*

The pharmacokinetic profile of niacin is complicated due to extensive first-pass metabolism that is dose-rate specific and, at the doses used to treat dyslipidemia, saturable. In humans, one pathway is through a simple conjugation step with glycine to form nicotinic 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

DN2011V1-proposed-niaspan-2009-sep-22

18 of 38

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.

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

### *Elimination*

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.

### **Pediatric Use**

No pharmacokinetic studies have been performed in this population ( $\leq 16$  years) [see *Use in Specific Populations (8.4)*].

### **Geriatric Use**

No pharmacokinetic studies have been performed in this population ( $> 65$  years) [see *Use in Specific Populations (8.5)*].

### **Renal Impairment**

No pharmacokinetic studies have been performed in this population. NIASPAN should be used with caution in patients with renal disease [see *Warnings and Precautions (5)*].

### **Hepatic Impairment**

No pharmacokinetic studies have been performed in this population. Active liver disease, unexplained transaminase elevations and significant or unexplained hepatic dysfunction are contraindications to the use of NIASPAN [see *Contraindications (4)* and *Warnings and Precautions (5.2)*].

### **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

DN2011V1-proposed-niaspan-2009-sep-22

19 of 38

metabolite. This 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. Recovery of niacin and metabolites in urine, however, is generally similar for men and women, indicating that absorption is similar for both genders [see *Gender (8.8)*].

## Drug interactions

### *Fluvastatin*

Niacin did not affect fluvastatin pharmacokinetics [see *Drug Interactions (7.1)*].

### *Lovastatin*

When NIASPAN 2000 mg and lovastatin 40 mg were co-administered, NIASPAN increased lovastatin  $C_{max}$  and AUC by 2% and 14%, respectively, and decreased lovastatin acid  $C_{max}$  and AUC by 22% and 2%, respectively. Lovastatin reduced NIASPAN bioavailability by 2-3% [see *Drug Interactions (7.1)*].

### *Simvastatin*

When NIASPAN 2000 mg and simvastatin 40 mg were co-administered, NIASPAN increased simvastatin  $C_{max}$  and AUC by 1% and 9%, respectively, and simvastatin acid  $C_{max}$  and AUC by 2% and 18%, respectively. Simvastatin reduced NIASPAN bioavailability by 2% [see *Drug Interactions (7.1)*].

### *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 [see *Drug Interactions (7.2)*].

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis and Mutagenesis and 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<sup>2</sup> 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.

## 14 CLINICAL STUDIES

#### 14.1 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.

Niacin's ability to reduce mortality and the risk of definite, nonfatal myocardial infarction (MI) has been assessed in long-term studies. The Coronary Drug Project, 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;  $p = \text{N.S.}$ ). 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%;  $p = 0.0004$ ). 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. 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;  $p < 0.0001$ ).

The Familial Atherosclerosis Treatment Study (FATS) in 146 men ages 62 and younger with Apo B levels  $\geq 125$  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. 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);

DN2011V1-proposed-niaspan-2009-sep-22

21 of 38

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. 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 and Precautions* (5.1)].

#### 14.2 NIASPAN Clinical Studies

##### *Placebo-Controlled Clinical Studies in Patients with Primary Hyperlipidemia and Mixed Dyslipidemia:*

In two randomized, double-blind, parallel, multi-center, placebo-controlled trials, NIASPAN dosed at 1000, 1500 or 2000 mg 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 3). Women appeared to have a greater response than men at each NIASPAN dose level (see *Gender Effect*, below).

**Table 3. 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 1000 mg at bedtime	41	-3	-5	+18	-17	-21	-13	-6	+9
NIASPAN 2000 mg at bedtime	41	-10	-14	+22	-25	-28	-27	-16	+8

DN2011V1-proposed-niaspan-2009-sep-22

22 of 38

Placebo	40	0	-1	+4	-3	0	0	+1	+3
NIASPAN 1500 mg at bedtime	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 2000 mg.

In a double-blind, multi-center, forced dose-escalation study, monthly 500 mg increases in NIASPAN dose resulted in incremental reductions of approximately 5% in LDL-C and Apo B levels in the daily dose range of 500 mg through 2000 mg (Table 4). Women again tended to have a greater response to NIASPAN than men (see *Gender Effect*, below).

**Table 4. 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								
500 mg at bedtime		-2	-3	+10	-10	-5	-3	-2	+5
1000 mg at bedtime		-5	-9	+15	-17	-11	-12	-7	+8
1500 mg at bedtime		-11	-14	+22	-26	-28	-20	-15	+10
2000 mg at bedtime		-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 500 mg, 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 1500 mg and 2000 mg, respectively.

Pooled results for major lipids from these three placebo-controlled studies are shown below (Table 5).

**Table 5. Selected Lipid Response to NIASPAN in Placebo-Controlled Clinical Studies\***

Mean Baseline and Median Percent Change from Baseline (25 <sup>th</sup> , 75 <sup>th</sup> Percentiles)				
NIASPAN Dose	n	LDL-C	HDL-C	TG
1000 mg at bedtime	104			
Baseline (mg/dL)		218	45	172
Percent Change		-7 (-15, 0)	+14 (+7, +23)	-16 (-34, +3)
1500 mg at bedtime	120			
Baseline (mg/dL)		212	46	171
Percent Change		-13 (-21, -4)	+19 (+9, +31)	-25 (-45, -2)
2000 mg at bedtime	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 hyperlipidemia and mixed dyslipidemia suggest that, at each NIASPAN dose level studied, changes in lipid concentrations are greater for women than for men (Table 6).

**Table 6. Effect of Gender on NIASPAN Dose Response**

NIASPAN Dose	n (M/F)	Mean Percent Change from Baseline							
		LDL-C		HDL-C		TG		Apo B	
		M	F	M	F	M	F	M	F
500 mg at bedtime	50/37	-2	-5	+11	+8	-3	-9	-1	-5
1000 mg at bedtime	76/52	-6*	-11*	+14	+20	-10	-20	-5*	-10*
1500 mg at bedtime	104/59	-12	-16	+19	+24	-17	-28	-13	-15
2000 mg at bedtime	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 2000 mg at bedtime) were compared to baseline in patients whose primary lipid abnormality was a low level of HDL-C (HDL-C  $\leq 40$  mg/dL, TG  $\leq 400$  mg/dL, and LDL-C  $\leq 160$ , or  $< 130$  mg/dL in the presence of CHD). Results are shown below (Table 7).

**Table 7. Lipid Response to NIASPAN in Patients with Low HDL-C**

	Mean Baseline and Mean Percent Change from Baseline*									
	n	TC	LDL-C	HDL-C	TC/HDL-C	TG	Lp(a) <sup>†</sup>	Apo B <sup>†</sup>	Apo A- Lp A-I <sup>††</sup>	Lp A-I <sup>††</sup>
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.

<sup>†</sup> n = 72 at baseline and 69 at week 19.

<sup>††</sup> n = 30 at baseline and week 19.

At NIASPAN 2000 mg/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.

### 14.3 NIASPAN and Lovastatin Clinical Studies

**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 500 mg/20 mg (expressed as mg of niacin/mg of lovastatin) once daily before bedtime. The dose was increased by 500 mg at 4-week

intervals (based on the NIASPAN component) to a maximum dose of 1000 mg/20 mg in one-half of the patients and 2000 mg/40 mg in the other half. The NIASPAN monotherapy group underwent a similar titration from 500 mg to 2000 mg. The patients randomized to lovastatin monotherapy received 20 mg for 12 weeks titrated to 40 mg 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 8, 9, 10, and 11). 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 40 mg only after 28 weeks of titration to a dose of 2000 mg/40 mg ( $p < 0.0001$ )
2. The combination tablet of NIASPAN and lovastatin at doses of 1000 mg/20 mg or higher achieved greater LDL-lowering than NIASPAN ( $p < 0.0001$ )

The LDL-C results are summarized in [Table 8](#).

**Table 8. 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 9](#)).

**Table 9. 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	61 – 43
						mg/dL	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 1000 mg/20mg or greater compared to lovastatin and NIASPAN monotherapy ([Table 10](#)).

**Table 10. 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	61 – 171
						mg/dL	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 11](#)). 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 11. 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	60	–	42
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

#### 14.4 NIASPAN and Simvastatin Clinical Studies

In a double-blind, randomized, multicenter, multi-national, active-controlled, 24-week study, the lipid effects of a combination tablet of NIASPAN and simvastatin were compared to simvastatin 20 mg and 80 mg in 641 patients with type II hyperlipidemia or mixed dyslipidemia. Following a lipid qualification phase, patients were eligible to enter one of two treatment groups. In Group A, patients on simvastatin 20 mg monotherapy, with elevated non-HDL levels and LDL-C levels at goal per the NCEP guidelines, were randomized to one of three treatment arms: combination tablet of NIASPAN and simvastatin 1000/20 mg, combination tablet of NIASPAN and simvastatin 2000/20 mg, or simvastatin 20 mg. In Group B, patients on simvastatin 40 mg monotherapy, with elevated non-HDL levels per the NCEP guidelines regardless of attainment of LDL-C goals, were randomized to one of three treatment arms: combination tablet of NIASPAN and simvastatin 1000/40 mg, combination tablet of NIASPAN and simvastatin 2000/40 mg, or simvastatin 80 mg. Therapy was initiated at the 500 mg dose of combination tablet of NIASPAN and simvastatin and increased by 500 mg every four weeks. Thus patients were titrated to the 1000 mg dose of combination tablet of NIASPAN and simvastatin after four weeks and to the 2000 mg dose of combination tablet of NIASPAN and simvastatin after 12 weeks. All patients randomized to simvastatin monotherapy received 50 mg

immediate-release niacin daily in an attempt to keep the study from becoming unblinded due to flushing in the combination tablet of NIASPAN and simvastatin groups. Patients were instructed to take one 325 mg aspirin or 200 mg ibuprofen 30 minutes prior to taking the double-blind medication to help minimize flushing effects.

In Group A, the primary efficacy analysis was a comparison of the mean percent change in non-HDL levels between the combination tablet of NIASPAN and simvastatin 2000/20 mg and simvastatin 20 mg groups, and if statistically significant, then a comparison was conducted between the combination tablet of NIASPAN and simvastatin 1000/20 mg and simvastatin 20 mg groups. In Group B, the primary efficacy analysis was a determination of whether the mean percent change in non-HDL in the combination tablet of NIASPAN and simvastatin 2000/40 mg group was non-inferior to the mean percent change in the simvastatin 80 mg group, and if so, whether the mean percent change in non-HDL in the combination tablet of NIASPAN and simvastatin 1000/40 mg group was non-inferior to the mean percent change in the simvastatin 80 mg group.

In Group A, the non-HDL-C lowering with combination tablet of NIASPAN and simvastatin 2000/20 and combination tablet of NIASPAN and simvastatin 1000/20 was statistically significantly greater than that achieved with simvastatin 20 mg after 24 weeks ( $p < 0.05$ ; [Table 12](#)). The completion rate after 24 weeks was 72% for the combination tablet of NIASPAN and simvastatin arms and 88% for the simvastatin 20 mg arm. In Group B, the non-HDL-C lowering with combination tablet of NIASPAN and simvastatin 2000/40 and combination tablet of NIASPAN and simvastatin 1000/40 was non-inferior to that achieved with simvastatin 80 mg after 24 weeks ([Table 13](#)). The completion rate after 24 weeks was 78% for the combination tablet of NIASPAN and simvastatin arms and 80% for the simvastatin 80 mg arm.

The combination tablet of NIASPAN and simvastatin was not superior to simvastatin in lowering LDL-C in either Group A or Group B. However, the combination tablet of NIASPAN and simvastatin was superior to simvastatin in both groups in lowering TG and raising HDL ([Tables 14 and 15](#)).

**Table 12. Non-HDL Treatment Response Following 24-Week Treatment Mean Percent Change from Simvastatin 20-mg Treated Baseline**

Group A	Combination Tablet of NIASPAN and Simvastatin 2000/20	Combination Tablet of NIASPAN and Simvastatin 1000/20	Simvastatin 20

Week	n <sup>a</sup>	Dose (mg/mg)	Non- HDL <sup>b</sup>	n <sup>a</sup>	Dose (mg/mg)	Non- HDL <sup>b</sup>	n <sup>a</sup>	Dose (mg/mg)	Non- HDL <sup>b</sup>
Baseline	56	–	163.1 mg/dL	108	–	164.8 mg/dL	102	–	163.7 mg/dL
4	52	500/20	-12.9%	86	500/20	-12.8%	91	20	-8.3%
8	46	1000/20	-17.5%	91	1000/20	-15.5%	95	20	-8.3%
12	46	1500/20	-18.9%	90	1000/20	-14.8%	96	20	-6.4%
24	40	2000/20	-19.5% <sup>†</sup>	78	1000/20	-13.6% <sup>†</sup>	90	20	-5.0%
Dropouts by week 24:	28.6%			27.8%			11.8%		

<sup>a</sup> n=number of subjects with values in the analysis window at each timepoint

<sup>b</sup> The percent change from baseline is the model-based mean from a repeated measures mixed model with no imputation for missing data from study dropouts.

<sup>†</sup> significant vs. simvastatin 20 mg at the primary endpoint (Week 24),  $p < 0.05$

**Table 13. Non-HDL Treatment Response Following 24-Week Treatment Mean Percent Change from Simvastatin 40-mg Treated Baseline**

Week	Combination Tablet of NIASPAN and Simvastatin 2000/40			Combination Tablet of NIASPAN and Simvastatin 1000/40			Simvastatin 80		
	n <sup>a</sup>	Dose (mg/mg)	Non- HDL <sup>b</sup>	n <sup>a</sup>	Dose (mg/mg)	Non- HDL <sup>b</sup>	n <sup>a</sup>	Dose (mg/mg)	Non- HDL <sup>b</sup>
Baseline	98	–	144.4 mg/dL	111	–	141.2 mg/dL	113	–	134.5 mg/dL
4	96	500/40	-6.0%	108	500/40	-5.9%	110	80	-11.3%
8	93	1000/40	-15.5%	100	1000/40	-16.2%	104	80	-13.7%
12	90	1500/40	-18.4%	97	1000/40	-12.6%	100	80	-9.5%

DN2011V1-proposed-niaspan-2009-sep-22

30 of 38

24	80	2000/40	-7.6% <sup>c</sup>	82	1000/40	-6.7% <sup>d</sup>	90	80	-6.0%
Dropouts	18.4%			26.1%			20.4%		

by week  
24:

<sup>a</sup> n=number of subjects with values in the analysis window at each timepoint

<sup>b</sup> The percent change from baseline is the model-based mean from a repeated measures mixed model with no imputation for missing data from study dropouts.

<sup>c</sup> non-inferior to simvastatin 80 arm; 95% confidence interval of mean difference in non-HDL for the combination tablet of NIASPAN and simvastatin 2000/40 vs. simvastatin 80 is (-7.7%, 4.5%)

<sup>d</sup> non-inferior to simvastatin 80 arm; 95% confidence interval of mean difference in non-HDL for combination tablet of NIASPAN and simvastatin 1000/40 vs. combination tablet of NIASPAN and simvastatin 80 is (-6.6%, 5.3%)

**Table 14. Mean Percent Change from Baseline to Week 24 in Lipoprotein Lipid Levels**

Treatment Group A						
TREATMENT	N	LDL-C	Total-C	HDL-C	TG <sup>a</sup>	Apo B
Baseline (mg/dL)*	266	120	207	43	209	102
Simvastatin 20 mg	102	-6.7%	-4.5%	7.8%	-	-5.6%
Combination Tablet of NIASPAN and Simvastatin 1000/20	108	-	-8.8%	20.7%	-	-
Combination Tablet of NIASPAN and Simvastatin 2000/20	56	-	-11.1%	29.0%	-	-
					15.3%	
					26.5%	13.2%
					38.0%	18.5%

\* either treatment naïve or after receiving simvastatin 20 mg

<sup>a</sup> medians are reported for TG

**Table 15. Mean Percent Change from Baseline to Week 24 in Lipoprotein Lipid Levels**

**Treatment Group B**

TREATMENT	N	LDL-C	Total- C	HDL- C	TG <sup>a</sup>	Apo B
Baseline (mg/dL)*	322	108	187	47	145	93
Simvastatin 80 mg	113	-	-6.2% 11.4%	0.1%	0.3%	-7.5%
Combination Tablet of NIASPAN and Simvastatin 1000/40	111	-7.1%	-3.1%	15.4%	-	-7.7% 22.8%
Combination Tablet of NIASPAN and Simvastatin 2000/40	98	-5.1	-1.6%	24.4%	-	- 31.8% 10.5%

\* after receiving simvastatin 40 mg

<sup>a</sup> medians are reported for TG

**16 HOW SUPPLIED/STORAGE AND HANDLING**

NIASPAN tablets are supplied as unscored, medium-orange, film-coated, capsule-shaped (containing 500 or 750 mg of niacin) or oval shaped (containing 1000 mg of niacin) tablets, in an extended-release formulation. Tablets are printed with the Abbott 'A' logo and the tablet strength (500, 750 or 1000). Tablets are supplied in bottles of 90 as shown below.

500 mg tablets: bottles of 90 - NDC# 0074-3074-90

750 mg tablets: bottles of 90 - NDC# 0074-3079-90

1000 mg tablets: bottles of 90 - NDC# 0074-3080-90

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

**17 PATIENT COUNSELING INFORMATION**

**17.1 Patient Counseling**

Patients should be advised to adhere to their National Cholesterol Education Program (NCEP) recommended diet, a regular exercise program, and periodic testing of a fasting lipid panel.

Patients should be advised to inform other healthcare professionals prescribing a new medication that they are taking NIASPAN.

DN2011V1-proposed-niaspan-2009-sep-22

32 of 38

The patient should be informed of the following:

### **Dosing Time**

NIASPAN tablets should be taken at bedtime, after a low-fat snack. Administration on an empty stomach is not recommended.

### **Tablet Integrity**

NIASPAN tablets should not be broken, crushed or chewed, but should be swallowed whole.

### **Dosing Interruption**

If dosing is interrupted for any length of time, their physician should be contacted prior to restarting therapy; re-titration is recommended.

### **Muscle Pain**

Notify their physician of any unexplained muscle pain, tenderness, or weakness promptly. They should discuss all medication, both prescription and over the counter, with their physician.

### **Flushing**

Flushing (warmth, redness, itching and/or tingling of the skin) is a common side effect of niacin therapy that may subside after several weeks of consistent NIASPAN use. Flushing may vary in severity and is more likely to occur with initiation of therapy, or during dose increases. By dosing at bedtime, flushing will most likely occur during sleep. However, if awakened by flushing at night, the patient should get up slowly, especially if feeling dizzy, feeling faint, or taking blood pressure medications.

### **Use of Aspirin Medication**

Taking aspirin approximately 30 minutes before dosing can minimize flushing.

### **Diet**

Avoid ingestion of alcohol, hot beverages and spicy foods around the time of taking NIASPAN to minimize flushing.

### **Supplements**

Notify their physician if they are taking vitamins or other nutritional supplements containing niacin or nicotinamide.

DN2011V1-proposed-niaspan-2009-sep-22

33 of 38

### **Dizziness**

Notify their physician if symptoms of dizziness occur.

### **Diabetics**

If diabetic, to notify their physician of changes in blood glucose.

### **Pregnancy**

Discuss future pregnancy plans with your patients, and discuss when to stop NIASPAN if they are trying to conceive. Patients should be advised that if they become pregnant, they should stop taking NIASPAN and call their healthcare professional.

### **Breastfeeding**

Women who are breastfeeding should be advised to not use NIASPAN. Patients, who have a lipid disorder and are breastfeeding, should be advised to discuss the options with their healthcare professional.

©2009 Abbott Laboratories

Manufactured for Abbott Laboratories, North Chicago, IL 60064, U.S.A.

500 mg NIASPAN tablets

by Norwich Pharmaceuticals, Inc., Norwich, NY 13815

or

500 mg, 750 mg and 1000 mg tablets

by Abbott Pharmaceuticals PR Ltd., Barceloneta, PR 00617

U.S. Patent Nos. 6,080,428; 6,129,930; 6,406,715 B1; 6,676,967; 6,746,691; 6,818,229; 7,011,848; 6,469,035 and other patents pending.

## **NIASPAN**

niacin tablet, film coated, extended release