NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) is available for oral administration as a bi-layer tablet containing 1 g of extended-release nicotinic acid and 20 mg of immediate-release laropiprant.

NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) contains extended-release nicotinic acid, which at therapeutic doses is a lipid-modifying agent, and laropiprant, a potent, selective antagonist of the prostaglandin D₂ (PGD₂) receptor subtype 1 (DP₁). Laropiprant suppresses PGD₂ mediated flushing associated with administration of nicotinic acid.

The chemical name of nicotinic acid is 3-pyridinecarboxylic acid. The empirical formula of nicotinic acid is C₆H₅NO₂ and its molecular weight is 123.11.

Nicotinic acid is a white powder that is soluble in water. Its structural formula is:

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N
O
OH
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The chemical name of laropiprant is [(3R)-4-(4-chlorobenzyl)-7-fluoro-5-(methylsulfonyl)-1,2,3,4-tetrahydrocyclopenta[b] indol-3-yl]acetic acid. The empirical formula is C₂₁H₁₉ClFNO₄S and its molecular weight is 435.90.
Laropiprant is a white powder that is soluble to very soluble in ethanol, methanol, acetonitrile, and acetone and insoluble in water. Its structural formula is:

![Structural formula of Laropiprant](image)

**PHARMACODYNAMICS**

**Nicotinic acid**

**Lipid Effects**
Clinical and epidemiologic studies demonstrate that high total cholesterol (TC), LDL-C, apo B, and TG promote human atherosclerosis and are risk factors for cardiovascular disease. In contrast, higher levels of HDL-C and apo A-I are associated with lower cardiovascular risk. Clinical studies have shown that lowering LDL-C decreases cardiovascular risk. Higher HDL2:HDL3 ratio is associated with decreased cardiovascular disease risk. HDL is hypothesized to participate in the reverse transport of cholesterol from tissues back to the liver, to suppress vascular inflammation associated with atherosclerosis, as well as to have anti-oxidative and anti-thrombotic effects.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. Lp(a) is a modified LDL particle also associated with increased cardiovascular disease risk. Elevated plasma TG levels 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 levels have not consistently been shown to be an independent risk factor for CHD. Small, dense LDL particles are thought to be the most atherogenic LDL particles.

Nicotinic acid in gram doses reduces the levels of LDL-C, total cholesterol, TG, VLDL-C, apo B (the major LDL protein), and Lp(a). Nicotinic acid also elevates the levels of HDL-C and its major protein component apo A-I. Nicotinic acid elevates the HDL2 subfraction to a greater extent than the HDL3 subfraction, thereby increasing the HDL2:HDL3 ratio. In addition, nicotinic acid has been shown to cause a relative shift in the distribution of LDL subclasses from small, dense to larger LDL particles. The clinical relevance of this effect requires further investigation.

**Laropiprant**

**Suppression of Nicotinic acid-induced Flushing**
Flushing associated with nicotinic acid is due to vasodilation of the skin and is characterized by redness of the skin, sensation of warmth, itching or tingling, particularly in the head, neck, and upper torso. Nicotinic acid-induced flushing is mediated primarily by PGD2 released by cells in the skin. Following a single oral dose of nicotinic acid, a substantial increase in plasma levels of 9α, 11β-PGF2, a metabolite of
PGD$_2$, coincided with the onset of flushing. Nicotinic acid does not increase histamine metabolites or the major urinary metabolite of prostaglandin E$_2$ (PGE$_2$).

Laropiprant is a potent and selective antagonist of the PGD$_2$ receptor subtype 1, DP$_1$, which has been shown in animal studies to be the primary pathway of nicotinic acid-induced flushing. Laropiprant has been shown to be effective in reducing flushing symptoms induced by nicotinic acid. The reduction in flushing symptoms (assessed by patient questionnaires) was correlated with a reduction in nicotinic acid-induced vasodilation (assessed by measurements of skin blood flow). In healthy subjects receiving NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE), pretreatment with aspirin 325 mg had no additional beneficial effects in reducing nicotinic acid-induced flushing symptoms compared to NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) alone. (See UNDESIRABLE EFFECTS.)

**Effects on Platelet Function**

Laropiprant is a potent and selective antagonist of the PGD$_2$ receptor, DP$_1$. However, it also has affinity for the thromboxane A$_2$ receptor (TP), although it is approximately 190-fold less potent at TP as compared to DP$_1$.

Platelet function was assessed in a number of studies with laropiprant. Therapeutic doses of laropiprant had no clinically relevant effect on measures of platelet function including bleeding time and collagen-induced platelet aggregation. A study demonstrated that laropiprant did not alter the antiplatelet effect of aspirin and did not affect bleeding time associated with aspirin. (See INTERACTIONS WITH OTHER MEDICAMENTS, Laropiprant.)

### PHARMACOKINETICS

#### Absorption

**Nicotinic acid**

Following a 2 g dose of nicotinic acid administered orally as two tablets of NICOTINIC ACID + LAROPI PRANT (TREDAPTIVE) with food, nicotinic acid was absorbed with a median time to peak plasma concentration (T$_{\text{max}}$) of 4 hours, a mean area under the plasma concentration-time curve (AUC$_{0-\text{last}}$) of approximately 58.0 μM·hr, and a mean peak plasma concentration (C$_{\text{max}}$) of approximately 20.2 μM. Bioavailability (with or without food) is at least 72% based on the recovery of the nicotinic acid dose in the urine. The oral bioavailability of nicotinic acid is not altered when it is taken with a high-fat meal.

**Laropiprant**

Following a 40 mg dose of laropiprant administered orally as two tablets of NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) with food, laropiprant was rapidly absorbed with a median T$_{\text{max}}$ of 1 hour, a mean AUC$_{0-\infty}$ of approximately 13 μM·hr, and a mean C$_{\text{max}}$ of approximately 1.6 μM. The rate and extent of absorption are not altered with a high-fat meal. The pharmacokinetics of laropiprant are linear, displaying approximately dose-proportional increases in AUC and C$_{\text{max}}$ and no evidence of time-dependent clearance.

The mean absolute bioavailability of laropiprant is approximately 71% following a 40 mg dose when administered as two tablets of NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) after an overnight fast.

#### Distribution

**Nicotinic acid**
Nicotinic is less than 20% bound to serum proteins.

**Laropiprant**
The mean volume of distribution at steady state following a single 40 mg intravenous dose of laropiprant to healthy subjects is approximately 70 liters. Laropiprant is highly bound (>99%) to plasma proteins and its binding is independent of concentration. Laropiprant crosses the placenta in rats and rabbits.

**Metabolism**

**Nicotinic acid**
Nicotinic acid undergoes extensive first-pass metabolism through two pathways that are dose and dose-rate dependent. The first pathway results in the formation of nicotinamide adenine dinucleotide (NAD) and nicotinamide. In humans, nicotinamide is further predominantly metabolized to N-methylnicotinamide (MNA) and to N-methyl-2-pyridone-5-carboxamide (2PY). In the second pathway, glycine is conjugated with nicotinic acid to form nicotinuric acid (NUA). With low doses of nicotinic acid or lower rates of absorption, the first pathway predominates. At higher doses or higher rates of absorption, the NAD pathway is saturable, and an increasing fraction of the oral dose reaches the bloodstream unchanged as nicotinic acid. The glycine conjugation pathway is not saturated across the clinically relevant dose range, based on the dose-proportional increase in the plasma concentrations of NUA from 1 g to 2 g.

**Laropiprant**
Laropiprant is metabolized primarily via acyl glucuronidation, with a smaller component of oxidative metabolism, followed by excretion of the glucuronide into feces (via bile) and urine. Laropiprant and its acyl glucuronide conjugate are the major circulating components in human plasma. In vitro studies have shown that the acyl glucuronide conjugate of laropiprant had at least a 65-fold reduced affinity for DP₁ as compared to laropiprant; thus, it is not expected to contribute to the overall DP₁ activity of laropiprant. The major component (73% of radioactivity) in feces is laropiprant (comprising unabsorbed drug and/or hydrolyzed glucuronic acid conjugate). In urine, the primary drug-related component is the acyl glucuronide conjugate (64% of radioactivity) with smaller contributions from the parent compound (5%). The oxidative metabolism of laropiprant is catalyzed primarily by CYP3A4, whereas several UGT isoforms (1A1, 1A3, 1A9 and 2B7) catalyzed the acyl glucuronidation.

**Elimination**

**Nicotinic acid**
Nicotinic acid is predominantly excreted in the urine as metabolites.

**Laropiprant**
Laropiprant is eliminated primarily via acyl glucuronidation, followed by excretion of the glucuronide in feces (via bile) and urine. Following oral administration of ¹⁴C-laropiprant in humans, approximately 68% of the dose was recovered in feces (primarily as parent compound, comprising unabsorbed drug and/or hydrolyzed glucuronic acid conjugate) and 22% was recovered in urine (primarily as metabolites). The majority of the dose was excreted within 96 hours. The apparent terminal half-life (t₁/₂) following a 40 mg dose of laropiprant administered as two tablets of NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) with food was approximately 17 hours. Pharmacokinetic steady state is achieved within 2 days of once-daily dosing of laropiprant, with minimal accumulation in AUC (approximately 1.3-fold) and Cₘₐₓ (approximately 1.1-fold).

**INDICATIONS**
• NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) is indicated to be used alone or in combination with HMG-CoA reductase inhibitors as an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), LDL-C:HDL-C ratio, non-HDL-C, apolipoprotein B (apo B), and increase high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-I (apo A-I) in patients with primary hypercholesterolemia (Fredrickson Type IIa\(^1\), heterozygous familial and non-familial) or mixed dyslipidemia (Fredrickson Type IIb\(^1\)).

• In patients with a history of myocardial infarction (MI) or coronary artery disease (CAD), nicotinic acid is indicated to reduce the risk of a recurrent nonfatal MI.

• In patients with dyslipidemia, nicotinic acid with an HMG-CoA reductase inhibitor or bile acid sequestrant is indicated to slow progression or promote regression of atherosclerosis.

• Nicotinic acid, alone or in combination with a bile acid sequestrant, is indicated as an adjunct to diet for the reduction of elevated total and LDL cholesterol levels in patients with hypercholesterolemia (Types IIa and IIb\(^1\)) when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate.

• Nicotinic acid is also indicated as adjunctive therapy for the treatment of adult patients with very high serum triglyceride levels (Types IV and V hyperlipidemia\(^1\)) 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 triglyceride levels over 2000 mg/dL and have elevations of very low density lipoprotein (VLDL) cholesterol as well as fasting chylomicrons (Type V hyperlipidemia\(^1\)). Subjects who consistently have total serum or plasma triglycerides below 1000 mg/dL are unlikely to develop pancreatitis. Therapy with nicotinic acid may be considered for those subjects with triglyceride 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 triglycerides under 1000 mg/dL may, through dietary or alcoholic indiscretion, convert to a Type V pattern with massive triglyceride elevations accompanying fasting chylomicronemia, but the influence of nicotinic acid therapy on the 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 triglycerides, but who have normal levels of VLDL. Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV, and V hyperlipoproteinemia.

### RECOMMENDED DOSE

NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) should be taken with food in the evening or at bedtime. The starting dose is one (1 g/20 mg) tablet once a day. After four weeks, it is recommended that patients be advanced to the maintenance dose of 2 g/40 mg taken as two (1 g/20 mg) tablets once daily. Daily doses greater than 2 g/40 mg have not been studied and therefore are not recommended.

\(^{1}\) Classification of Hyperlipoproteinemias

<table>
<thead>
<tr>
<th>Type</th>
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<td>TG</td>
<td>↑→C</td>
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<tr>
<td>IIa</td>
<td>LDL</td>
<td>C</td>
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<tr>
<td>IIb</td>
<td>LDL, VLDL</td>
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<td>III (rare)</td>
<td>IDL</td>
<td>TG</td>
<td>↑→C</td>
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<tr>
<td>IV</td>
<td>VLDL</td>
<td>TG</td>
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<tr>
<td>V (rare)</td>
<td>chylomicrons, VLDL</td>
<td>TG</td>
<td>↑→C</td>
<td></td>
</tr>
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</table>

C = cholesterol, TG = triglycerides, LDL = low-density lipoprotein, VLDL = very-low-density lipoprotein, IDL = intermediate-density lipoprotein.
NICOTINIC ACID+ LAROPIPRANT (TREDAPTIVE) should be taken whole. To preserve the extended-release properties, do not split, break, crush, or chew the tablet before swallowing. To reduce the possibility of flushing, patients may want to avoid drinking alcohol or hot drinks or eating spicy foods near the time of taking NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE).

If NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) is missed for <7 consecutive days, patients can reinstitute therapy at the last administered dosage. If NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) is missed for ≥7 consecutive days, reinstitution of therapy should begin at the 1 g/20 mg dose for 1 week, before advancing to the maintenance dose of 2 g/40 mg.

Those patients switching from 2 g or more of another modified-release nicotinic acid product can initiate NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) at the 2 g/40 mg dose. Patients switching from less than 2 g of another modified-release nicotinic acid product should initiate NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) at the starting dose of 1 g/20 mg. For patients switching from immediate-release nicotinic acid to NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE), therapy with NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) should be initiated at the 1 g/20 mg dose and advanced to the 2 g/40 mg maintenance dose after four weeks.

Use in the Elderly
No dosage adjustment is required for elderly patients.

Use in Pediatric Patients
Safety and effectiveness of NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) in pediatric patients have not been established. Therefore, treatment with NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) is not recommended.

Use in Patients with Hepatic or Renal Insufficiency
Use of NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) in patients with hepatic or renal insufficiency has not been studied. Like other nicotinic acid products, NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) is contraindicated in patients with significant or unexplained hepatic dysfunction. NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) should be used with caution in patients with renal insufficiency, because nicotinic acid and its metabolites are primarily excreted by the kidneys. (See CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS).

Concomitant Therapy
NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) may be administered with an HMG-CoA reductase inhibitor (statin) for additional lipid-altering effect (see WARNINGS AND PRECAUTIONS). In a clinical trial, 1072 patients receiving NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE), the nicotinic acid component of NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE), or placebo were also taking statins (29% atorvastatin, 54% simvastatin, 17% other statins (pravastatin, fluvastatin, rosuvastatin, lovastatin), of which 9% were also taking ezetimibe.

Aspirin provides no additional reduction of flushing beyond that achieved by NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE). Therefore, treatment with aspirin to alleviate flushing symptoms is not necessary.

Because coadministration of bile acid sequestrants may reduce the bioavailability of acidic drugs such as nicotinic acid, it is recommended that NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) be administered >1 hour before or >4 hours after administration of a bile acid sequestrant.
NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) should be taken with food in the evening or at bedtime. The starting dose is one (1 g/20 mg) tablet once a day. After four weeks, it is recommended that patients be advanced to the maintenance dose of 2 g/40 mg taken as two (1 g/20 mg) tablets once daily. Daily doses greater than 2 g/40 mg have not been studied and therefore are not recommended.

NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) should be taken whole. To preserve the extended-release properties, do not split, break, crush, or chew the tablet before swallowing. To reduce the possibility of flushing, patients may want to avoid drinking alcohol or hot drinks or eating spicy foods near the time of taking NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE).

### CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients.
- Significant or unexplained hepatic dysfunction.
- Active peptic ulcer disease.
- Arterial bleeding.

### WARNINGS AND PRECAUTIONS

**Hepatic Effects**

Switching from immediate-release (crystalline) nicotinic acid to NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) has not been studied. However, cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have switched from immediate-release nicotinic acid to sustained-release (modified-release, timed-release) nicotinic acid products at equivalent doses. Therefore, patients switching from immediate-release nicotinic acid to NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) should be initiated at the 1 g/20 mg dose.

NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Significant or unexplained hepatic dysfunction is a contraindication to the use of NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE).

Like other lipid-lowering therapies, nicotinic acid products have been associated with abnormal liver function tests. In studies where 2548 patients were randomized to receive NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) for 12 to 52 weeks (8 to 48 weeks at the 2 g/40 mg dose), the overall incidence of consecutive elevations (≥3X the upper limit of normal (ULN) in ALT and/or AST was 1.0% and was not significantly different from nicotinic acid (pooled extended-release formulations) or pooled placebo/simvastatin (0.5% and 0.9%, respectively). Transaminase elevations were reversible upon discontinuation of NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE).

Liver function tests are recommended before initiation, every 6 to 12 weeks for the first year, and periodically (e.g., semiannually) thereafter. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of ≥3X ULN persist, reduction of dose or withdrawal of NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) is recommended.

**Effect on Skeletal Muscle**

Myopathy and rhabdomyolysis are known adverse reactions to statins and other lipid-lowering drugs. Rare cases of myopathy/rhabdomyolysis have been associated with concomitant administration of lipid-altering doses (≥1 g/day) of nicotinic acid and HMG-CoA reductase inhibitors (statins). In worldwide,
multinational studies where 2548 patients (78% Caucasian, 12% Hispanic, 4% Black, 6% Other) were randomized to receive NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) for 12 to 52 weeks (8 to 48 weeks at the 2 g/40 mg dose; 1601 of whom were also taking statins), the overall incidence of creatine kinase (CK) ≥10X ULN was 0.3% and was not significantly different from nicotinic acid (pooled extended-release formulations) or pooled placebo/simvastatin (0.2% and 0.2%, respectively). In these studies, there was no excess of myopathy or rhabdomyolysis associated with NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) compared with the relevant control arm (placebo or statin alone).

In an ongoing, double-blind, randomized cardiovascular outcomes trial conducted in China, the United Kingdom and Scandinavia, an interim analysis by the independent safety monitoring committee revealed that the incidence of myopathy among approximately 4700 UK/Scandinavian patients treated with NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) 2 g/40 mg coadministered with either simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg is similar to the overall incidence of 0.08% reported in the prescribing information for simvastatin 40 mg. However, in approximately 3900 Chinese patients in the same treatment arm, the incidence is higher than expected (approximately 0.9%). The risk of myopathy was not increased among 8600 Chinese, UK, or Scandinavian patients in the control arm (placebo plus simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg).

Physicians contemplating combined therapy with statins and NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) 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 when the dosage of either drug is increased. Periodic serum CK should be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Because the incidence of myopathy is higher than expected in Chinese patients, caution should be used when treating Chinese patients with NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) coadministered with simvastatin or ezetimibe/simvastatin (particularly simvastatin doses of 40 mg or higher). Because the risk of myopathy with statins is dose-related, the use of NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) with simvastatin 80 mg or ezetimibe/simvastatin 10/80 mg is not recommended in Chinese patients. It is unknown whether there is an increased risk of myopathy in other Asian patients treated with NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) coadministered with simvastatin or ezetimibe/simvastatin.

Renal Dysfunction
Because nicotinic acid and its metabolites are excreted through the kidneys, NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) should be used with caution in patients with renal dysfunction.

Effect on Glucose
Nicotinic acid preparations have been associated with increases in fasting blood glucose levels. In a 24-week clinical trial, the median increase in blood glucose levels was 4 mg/dL at the end of treatment in patients exposed to NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) (n=798) or the nicotinic acid component of NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) (n=541) alone. Observed median increases in HbA1c in diabetic patients taking NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) (n=136) or nicotinic acid (n=78) alone were 0.2% and 0.1%, respectively (where modification of hypoglycemic therapy was allowed). Diabetic or potentially diabetic patients should be observed closely. Adjustment of diet and/or hypoglycemic therapy may be necessary.

Acute Coronary Syndrome
As with other nicotinic acid products, caution should be used when NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) 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.
Hematologic Effects
As with other nicotinic acid products, NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) was associated with small reductions in platelet count. The mean percent change from baseline reported in a clinical trial with NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) 2 g/40 mg was -14.0% at Week 24. NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) was not associated with an increase in prothrombin time. Nevertheless, patients undergoing surgery should be carefully evaluated.

Effect on Uric Acid
As with other nicotinic acid products, NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) was associated with small increases in uric acid levels. The mean percent change from baseline reported in a clinical trial with NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) 2 g/40 mg was +14.7% at Week 24. Therefore, NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) should be used with caution in patients with or predisposed to gout.

INTERACTIONS WITH OTHER MEDICAMENTS

Nicotinic acid

Effects of Nicotinic acid on Other Drugs

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

HMG-CoA Reductase Inhibitors: (See WARNINGS AND PRECAUTIONS, Effect on Skeletal Muscle)

CYP: In in vitro studies, nicotinic acid and its metabolites (nicotinuric acid (NUA), methyl nicotinamide (MNA), and 1-methyl-2-pyridone-5-carboxamide (2PY) did not inhibit CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4-mediated reactions or UGT1A1-mediated 3-glucuronidation of estradiol.

Effects of Other Drugs on Nicotinic acid

Bile Acid Sequestrants: Because coadministration of bile acid sequestrants may reduce the bioavailability of acidic drugs such as nicotinic acid, it is recommended that NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) be administered >1 hour before or >4 hours after administration of a bile acid sequestrant.

Supplements Containing Nicotinic Acid: Vitamins or other nutritional supplements containing large doses of nicotinic acid (or nicotinamide) have not been studied with NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE). Physicians should consider the nicotinic acid intake from vitamins and nutritional supplements when prescribing NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE).

Drug/Laboratory Test Interactions: In urine glucose tests, nicotinic acid may give false-positive reactions with cupric sulfate solution (Benedict's reagent).

Laropiprant

Effects of Laropiprant on Other Drugs

Midazolam: Multiple doses of laropiprant did not affect the pharmacokinetics of midazolam, a sensitive CYP3A4 substrate. Therefore, laropiprant is not an inducer or inhibitor of CYP3A4. Although laropiprant did not affect the pharmacokinetics of midazolam through CYP3A4, the plasma concentration of a metabolite of midazolam, 1'hydroxymidazolam, was increased approximately 2-fold with multiple doses of laropiprant. Because 1'hydroxymidazolam is an active metabolite, the pharmacodynamic activity of midazolam may be increased and caution should be used when laropiprant is coadministered with midazolam.

Other Drugs: 1'hydroxymidazolam is metabolized predominantly by uridine diphosphate-glucuronosyltransferases (UGT) 2B4 and 2B7. Clinical studies and in vitro studies support the conclusion
that laropiprant is a mild to moderate inhibitor of UGT2B4/UGT2B7. Very few drugs are known to be metabolized predominantly by UGT2B4 or UGT2B7. Although interactions with these drugs are generally <2-fold in magnitude, caution should be used when NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) is coadministered with drugs metabolized predominantly by UGT2B4 or UGT2B7 (e.g., azidothymidine (AZT)).

In interactions with other medicaments studies, laropiprant did not have clinically meaningful effects on the pharmacokinetics of the following: simvastatin, warfarin, oral contraceptives, rosiglitazone and digoxin. Based on these data, laropiprant is not expected to cause interactions with other medicaments with substrates of CYP isozymes 3A4, 2C9, 2C8 and human p-glycoprotein. In in vitro studies, laropiprant did not inhibit CYP1A2, CYP2B6, CYP2C19, CYP2D6, or CYP2E1-mediated reactions.

**Clopidogrel:** In a clinical study, there was no meaningful effect of laropiprant on the inhibition of ADP-induced platelet aggregation by clopidogrel, but there was a modest increase in the inhibition of collagen-induced platelet aggregation by clopidogrel. The clinical significance of these observations is unknown. A clinical study of laropiprant given with aspirin and clopidogrel has not been conducted. However, laropiprant did not alter the antiplatelet effect of aspirin (see PHARMACODYNAMICS, Effects on Platelet Function). Therefore, laropiprant would not be expected to have an additive effect on platelets in patients who are taking both aspirin and clopidogrel.

**Aspirin:** In a clinical study, concomitant administration of laropiprant with aspirin did not have an effect on collagen-induced platelet aggregation or on bleeding time compared to treatment with aspirin alone (see PHARMACODYNAMICS, Effects on Platelet Function).

**Effects of Other Drugs on Laropiprant.**

**CYP3A4 Inhibitors:** Clarithromycin (a potent inhibitor of CYP3A4) did not have a clinically meaningful effect on the pharmacokinetics of laropiprant. Therefore, CYP3A4 inhibitors are not expected to have a clinically significant impact on the pharmacokinetics of laropiprant.

**PREGNANCY AND LACTATION**

**NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE)**

Animal reproduction studies have not been conducted with NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE). It is not known whether NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) should be given to a pregnant woman only if clearly needed.

**Nicotinic acid**

Animal reproduction and developmental studies have not been conducted with nicotinic acid.

**Laropiprant**

Laropiprant was not teratogenic in rats up to doses of 100 mg/kg/day or in rabbits up to doses of 125 mg/kg/day (153 and 438 times the human exposure based on the AUC of the recommended daily adult human dose of laropiprant in two tablets of NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE). Slight decreases in mean maternal weight gain and fetal body weight, slight increases in pup mortality, and increased incidence of supernumerary rib and incomplete ossification of the sternebra in the fetus were observed at oral doses of 400 mg/kg/day in rats (513 times the human exposure based on the AUC of the recommended daily adult human dose of laropiprant in two tablets of NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE).

Because many drugs are excreted in human milk, caution should be exercised when NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) is administered to a nursing woman. No studies in lactating animals
have been conducted with NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE). Nicotinic acid has been reported to be excreted in human breast milk, but it is not known whether laropiprant is excreted in human breast milk. Studies in rats have shown that laropiprant is secreted in the milk.

**PEDIATRIC USE**

Safety and effectiveness of NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) in pediatric patients have not been established.

**USE IN THE ELDERLY**

In clinical studies of 2548 patients, the safety of NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) in the elderly (≥65 years, n=662) was comparable to that seen in younger patients (<65 years, n=1886). No dosage adjustment is required for elderly patients. The placebo-adjusted lipid responses for LDL-C, HDL-C and TG appeared larger in the elderly.

**UNDESIRABLE EFFECTS**

*Clinical Trials Experience*

NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) is generally well tolerated. Adverse reactions have usually been mild and transient.

**Flushing**

Flushing is the most common side effect of NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE). Flushing is most prominent in the head, neck, and upper torso.

In a pool of four active- or placebo-controlled clinical trials (N=4747, n=2548 taking NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE)), flushing was reported by the investigator as a possibly, probably, or definitely drug-related adverse reaction in 12.3% of patients taking NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE). In these studies, the percentage of patients taking NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE), nicotinic acid (pooled extended-release formulations), or pooled placebo/simvastatin who discontinued due to any flushing-related symptom (redness, warmth, itching and tingling) was 7.2%, 16.6%, and 0.4%, respectively. Discontinuations due to other specific adverse reactions among patients taking NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) were infrequent (<1%).

Flushing was evaluated as a primary endpoint in two large clinical studies. The first study measured a composite of flushing symptoms (redness, warmth, itching and tingling) reported by patients using an electronic diary. In this 24-week, placebo-controlled study, patients recorded flushing symptom severity associated with NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) (1 g/20 mg per day for Weeks 1-4; 2 g/40 mg per day for Weeks 5-24), the nicotinic acid component of NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) (1 g per day for Weeks 1-4; 2 g per day for Weeks 5-24) or placebo (Weeks 1-24). Patients taking NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) experienced significantly less flushing compared to nicotinic acid both in the first week of therapy (see Table 1), as well as over the 24-week study (see Figure 1). With advancement of NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) to the 2 g/40 mg dose and nicotinic acid to the 2 g dose at Week 5, there was a transient increase in incidence (Figure 1, panel A) and frequency (Figure 1, panel B) of moderate or greater flushing. In patients continuing in the study, the incidence and frequency of moderate or greater flushing in patients treated with NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) declined and approached that of patients receiving placebo, whereas in patients treated with nicotinic acid, the flushing incidence and frequency remained constant (after Week 6). (See Figure 1.)
<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Maximum Flushing Symptoms during Initiation (Week 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None or Mild</td>
</tr>
<tr>
<td>NICOTINIC ACID* 1 g (N=529)</td>
<td>44.0</td>
</tr>
<tr>
<td>NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) 1 g/20 mg (N=781)</td>
<td>68.9</td>
</tr>
<tr>
<td>Placebo (N=262)</td>
<td>93.9</td>
</tr>
</tbody>
</table>

* Nicotinic acid component of NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE)

Flushing was also evaluated as a primary endpoint in a 16-week study comparing NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) (one-step dosing regimen of 1 g/20 mg for 4 weeks advanced to 2 g/40 mg for 12 weeks) to NIASPAN® (a 12-week multi-step titration of 0.5 g for 4 weeks advanced in 0.5 g increments every 4 weeks to 2 g for the last 4 weeks). Both groups had the option of using aspirin to mitigate flushing. Patients taking NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) experienced significantly fewer days per week with moderate or greater flushing throughout the 16-week study (p<0.001).

**Overall Adverse Reactions with NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE)**

In addition to flushing, the following drug-related adverse reactions (reported by the investigator as possibly, probably, or definitely drug-related) were seen in controlled clinical trials in ≥1% of patients:

2 Registered Trademark of Merck, Inc.
treated with NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) for up to one year (with or without a statin):

Gastrointestinal disorders: diarrhea, dyspepsia, nausea, vomiting

General disorders and administration site conditions: feeling hot

Nervous system disorders: dizziness, headache, paresthesia

Skin and subcutaneous tissue disorders: erythema, pruritus, rash, urticaria

Hypersensitivity reactions: An apparent hypersensitivity reaction has been reported (<1%) characterized by multiple symptoms that may include: angioedema, pruritus, erythema, paresthesia, loss of consciousness, vomiting, urticaria, flushing, dyspnea, nausea, incontinence of urine and stool, cold sweats, shivering, chills, increased blood pressure, lip swelling, burning sensation, drug eruption, arthralgia, leg swelling, and tachycardia.

Laboratory Tests
Marked and persistent increases of serum transaminases have been reported infrequently (see WARNINGS AND PRECAUTIONS, Hepatic Effects). In controlled clinical studies, the incidence of clinically important elevations in serum transaminases (alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥3X ULN, consecutive) was 1.0% for patients treated with NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) with or without a statin. These elevations were generally asymptomatic and returned to baseline after discontinuation of therapy or with continued treatment.

Clinically important elevations of CK (≥10X ULN) were seen in 0.3% of the patients treated with NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) with or without a statin (see WARNINGS AND PRECAUTIONS, Effect on Skeletal Muscle).

Other abnormal laboratory values reported were elevations in LDH, fasting glucose, uric acid, total bilirubin, and amylase, and reductions in phosphorus and platelet counts (see WARNINGS AND PRECAUTIONS).

Nicotinic Acid-related Adverse Reactions
The following nicotinic acid-related adverse reactions have been seen in clinical trials or post-marketing experience with other nicotinic acid products or in <1% of patients taking NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) (or the nicotinic acid component of NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) in clinical trials:

Cardiac disorders: atrial fibrillation and other cardiac arrhythmias, palpitations, tachycardia

Eye disorders: cystoid macular edema, toxic amblyopia

Gastrointestinal disorders: abdominal pain, mouth edema, eructation, peptic ulcer

General disorders and administration site conditions: asthenia, chills, face edema, generalized edema, pain, peripheral edema

Hepatobiliary disorders: jaundice

Immune system disorders: angioedema, type I hypersensitivity

Infections and infestations: rhinitis

Metabolism and nutrition disorders: glucose tolerance impaired, gout

Musculoskeletal and connective tissue disorders: muscular weakness, myalgia

Nervous system disorders: migraine, syncope

Psychiatric disorders: anxiety, insomnia

Respiratory, thoracic, and mediastinal disorders: dyspnea

Skin and subcutaneous tissue disorders: acanthosis nigricans, dry skin, hyperpigmentation, macular rash, sweating (night or cold sweat), vesicular rash
Vascular disorders: hypotension, orthostatic hypotension

OVERDOSE AND TREATMENT

NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE)
In the event of an overdose, it is reasonable to employ the usual symptomatic and supportive measures. Cases of overdosage have been reported; the maximum dose of NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) taken was 5 g/100 mg. All patients recovered without sequelae.

Nicotinic acid
For an overdose of nicotinic acid, supportive measures should be employed.

Laropiprant
During controlled clinical trials in healthy subjects, single doses of up to 900 mg laropiprant and multiple doses up to 450 mg once daily for 10 days were generally well tolerated. There is no experience with doses of laropiprant above 900 mg in humans. Prolongation of collagen-induced platelet aggregation was observed in subjects taking multiple doses of 300 mg or greater (see PHARMACODYNAMICS, Effects on Platelet Function).

STORAGE CONDITION

Store at temperatures not exceeding 30°C. Store in the original package until time of use. Protect from light and moisture.

DOSAGE FORMS AND PACKAGING AVAILABLE

NICOTINIC ACID + LAROPIPRANT (TREDAPTIVE) is available in aluminum/aluminum blister pack of 7s, box of 28 tablets.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without the prescription of a physician.

DATE OF REVISION OF PACKAGE INSERT

PHL-MK0524A-T-082009