

Name of Medicine

TREDAPTIVE™

ER nicotinic acid/laropiprant

1 g/20 mg modified release tablet

Presentation

TREDAPTIVE comes as a white to off-white bi-layer capsule-shaped modified release tablet debossed with 552 on one side.

Therapeutic Class

TREDAPTIVE tablets contain ER (extended-release) nicotinic acid (niacin) and laropiprant.

Nicotinic Acid

- ER nicotinic acid at therapeutic doses is a lipid-modifying agent.
- In patients with a history of myocardial infarction (MI) or coronary artery disease (CAD), nicotinic acid has been shown in clinical studies to reduce the risk of a recurrent nonfatal MI.
- In patients with dyslipidaemia, nicotinic acid with an HMG-CoA reductase inhibitor or bile acid sequestrant has been shown in clinical studies to slow progression or promote regression of atherosclerosis.
- Nicotinic acid, alone or in combination with a bile acid sequestrant, and as an adjunct to diet, has been shown in clinical studies to reduce elevated total and LDL cholesterol levels in patients with hypercholesterolaemia (Types IIa and IIb)¹ when the response to a diet restricted in saturated fat and cholesterol and other non-pharmacologic measures alone has been inadequate.
- Nicotinic acid has also been used effectively in clinical studies as adjunctive therapy for the treatment of adult patients with very high serum triglyceride levels (Types IV and V hyperlipidaemia¹) 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 hyperlipidaemia¹). 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 chylomicronaemia, but the influence of nicotinic acid therapy on the risk of pancreatitis in such situations has not been adequately studied. Nicotinic acid therapy is not indicated for patients with Type I hyperlipoproteinaemia, 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 hyperlipoproteinaemia.

Laropiprant

Laropiprant is a potent, selective antagonist of the prostaglandin D₂ (PGD₂) receptor, DP₁. Laropiprant suppresses PGD₂ mediated flushing associated with administration of nicotinic acid.

Indications

- 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 hypercholesterolaemia (Fredrickson Type IIa¹, heterozygous familial and non-familial) or mixed dyslipidaemia (Fredrickson Type IIb¹).
- Prior to initiating therapy with TREDAPTIVE, secondary causes of hypercholesterolemia (e.g poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other medicine therapy, alcoholism) should be identified and treated.

Dosage and Administration

TREDAPTIVE (ER nicotinic acid/laropiprant) 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.

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 TREDAPTIVE.

If TREDAPTIVE is missed for < 7 consecutive days, patients can reinstitute therapy at the last administered dosage. If TREDAPTIVE is missed for ≥7 consecutive days, reinstatement 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 TREDAPTIVE at the 2 g/40 mg dose. Patients switching from less than 2 g of another modified-release nicotinic acid product should initiate TREDAPTIVE at the starting dose of 1 g/20 mg. For patients switching from immediate-release nicotinic acid to TREDAPTIVE, therapy with 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.

¹ Classification of Hyperlipoproteinaemias

Type	Lipoproteins <u>elevated</u>	Lipid Elevations	
		<u>major</u>	<u>minor</u>
I (rare)	chylomicrons	TG	↑→C
IIa	LDL	C	—
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C/TG	—
IV	VLDL	TG	↑→C
V (rare)	chylomicrons, VLDL	TG	↑→C

C = cholesterol, TG = triglycerides,
LDL = low-density lipoprotein,
VLDL = very-low-density lipoprotein,
IDL = intermediate-density lipoprotein.

Use in Paediatric Patients

Safety and effectiveness of TREDAPTIVE in paediatric patients have not been established. Therefore, treatment with TREDAPTIVE is not recommended.

Use in Patients with Hepatic or Renal Insufficiency

Use of TREDAPTIVE in patients with hepatic or renal insufficiency has not been studied. Like other nicotinic acid products, TREDAPTIVE is contraindicated in patients with significant or unexplained hepatic dysfunction. 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, and Warnings and Precautions, and Pharmacokinetics, *Characteristics in Patients*.)

Concomitant Therapy

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 TREDAPTIVE, ER nicotinic acid, 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 TREDAPTIVE. Therefore, treatment with aspirin to alleviate flushing symptoms is not necessary (see Actions, *Pharmacodynamics*).

Because co-administration of bile acid sequestrants may reduce the bioavailability of acidic medicines such as nicotinic acid, it is recommended that TREDAPTIVE be administered >1 hour before or >4 hours after administration of a bile acid sequestrant.

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 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 TREDAPTIVE should be initiated at the 1 g/20 mg dose.

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 TREDAPTIVE.

Like other lipid-lowering therapies, nicotinic acid products have been associated with abnormal liver function tests. In studies where 2548 patients were randomised to receive TREDAPTIVE for 12 to 52 weeks (8 to 48 weeks at the 2 g/40 mg dose), the overall incidence of consecutive elevations ($\geq 3X$ 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 TREDAPTIVE.

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

Effect on Skeletal Muscle

Myopathy and rhabdomyolysis are known adverse reactions to statins and other lipid-lowering medicines. 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 randomised to receive 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) $\geq 10X$ 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 TREDAPTIVE compared with the relevant control arm (placebo or statin alone).

In an ongoing, double-blind, randomised 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 TREDAPTIVE 2 g/40 mg co-administered 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 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 medicine 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 TREDAPTIVE co-administered 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 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 TREDAPTIVE co-administered with simvastatin or ezetimibe/simvastatin.

Renal Dysfunction

Because nicotinic acid and its metabolites are excreted through the kidneys, 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 TREDAPTIVE (n=798) or ER nicotinic acid (n=541) alone. Observed median increases in HbA1c in diabetic patients taking TREDAPTIVE (n=136) or ER nicotinic acid (n=78) alone were 0.2% and 0.1%, respectively (where modification of hypoglycaemic therapy was allowed). Diabetic or potentially diabetic patients should be observed closely. Adjustment of diet and/or hypoglycaemic therapy may be necessary.

Acute Coronary Syndrome

As with other nicotinic acid products, caution should be used when TREDAPTIVE is used in patients with unstable angina or in the acute phase of an MI, particularly when such patients are also receiving vasoactive medicines such as nitrates, calcium channel blockers, or adrenergic blocking agents.

Haematologic Effects

As with other nicotinic acid products, TREDAPTIVE was associated with small reductions in platelet count. The mean percent change from baseline reported in a clinical trial with TREDAPTIVE 2 g/40 mg was -14.0% at Week 24. TREDAPTIVE was not associated with an increase in prothrombin time (see Actions, *Pharmacodynamics*). Nevertheless, patients undergoing surgery should be carefully evaluated.

Effect on Uric Acid

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

Pregnancy

TREDAPTIVE

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

Nicotinic Acid

Nicotinic acid was not teratogenic in rats up to doses of 300 mg/kg/day or in rabbits up to doses of 300 mg/kg/day (253 and 104 times the human AUC of nicotinic acid based on the recommended daily dose of ER nicotinic acid in two tablets of TREDAPTIVE). Slight decreases in mean maternal weight gain and foetal body weight, slight decrease in ossification of the sacrocaudal vertebrae, and increased incidence of incomplete ossification of the cervical vertebra, sternbra, and hyoid in the foetus were observed at oral doses of 1000 mg/kg/day in rats (at least 959 times the human AUC of nicotinic acid based on the recommended daily dose of ER nicotinic acid in two tablets of TREDAPTIVE). Similar treatment-related changes were observed at oral doses of 900 mg/kg/day in rabbits (at least 629 times the human AUC of nicotinic acid based on the recommended daily dose of ER nicotinic acid in two tablets of TREDAPTIVE).

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 TREDAPTIVE).

Slight decreases in mean maternal weight gain and foetal body weight, slight increases in pup mortality, and increased incidence of supernumerary rib and incomplete ossification of the sternbra in the foetus 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 TREDAPTIVE).

Nursing Mothers

Because many medicines are excreted in human milk, caution should be exercised when TREDAPTIVE is administered to a nursing woman. No studies in lactating animals have been conducted with 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.

Paediatric Use

Safety and effectiveness of TREDAPTIVE in paediatric patients have not been established.

Use in the Elderly

In clinical studies of 2548 patients, the safety of 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.

Animal Toxicology

Acute Toxicity

Nicotinic Acid

The oral LD₅₀ of nicotinic acid in mice and rats is between 5000 and 7000 mg/kg.

Laropiprant

The oral LD₅₀ in mice is 1224 mg/kg. This dose is equivalent to up to 148 times the human exposure based on the recommended daily adult human dose of laropiprant in two tablets of TREDAPTIVE on a mg/m² basis. No mortality was observed in mice at 1000 mg/kg after a single dose of laropiprant. The oral LD₅₀ of laropiprant in female rats is 1591 mg/kg. This dose is equivalent to up to 387 times the human exposure based on the recommended daily adult human dose of laropiprant in two tablets of TREDAPTIVE on a mg/m² basis. No mortality was observed in rats at 800 mg/kg after a single dose of laropiprant.

Chronic Toxicity

TREDAPTIVE

The safety of concomitant administration of nicotinic acid and laropiprant was assessed in dogs and rats. In rats, 300 mg/kg/day of nicotinic acid was co-administered with 180 mg/kg/day of laropiprant for up to 6 months. In dogs, 200 mg/kg/day of nicotinic acid was co-administered with 150 mg/kg/day of laropiprant for up to 6 months. Toxicologic findings in these co-administration studies in rats and dogs were consistent with those seen with nicotinic acid and laropiprant administered individually.

Nicotinic Acid

Nicotinic acid was evaluated in rats following 6 months of dosing. Administration of nicotinic acid at a dose of 300 mg/kg/day produced degeneration in the stomach and hepatocyte vacuolation. This represents at least 179 times the human AUC of nicotinic

acid based on the recommended daily dose of ER nicotinic acid in two tablets of TREDAPTIVE.

Nicotinic acid was evaluated in dogs following 6 months of dosing. Administration of nicotinic acid at a dose of 200 mg/kg/day produced retinopathy and/or corneal lesions. This represents at least 240 times the human AUC of nicotinic acid based on the recommended daily dose of ER nicotinic acid in two tablets of TREDAPTIVE.

Laropiprant

Laropiprant was evaluated in a series of repeated dose toxicity studies for up to 6 months in rats. After 6 months of dosing at 180 mg/kg/day, ketonuria and hepatocellular centrilobular hypertrophy were observed. The hepatocellular centrilobular hypertrophy was consistent with rodent specific enzyme induction. The no-observed-adverse-effect level was 60 mg/kg/day. This represents at least 118 times the human exposure based on the AUC of the recommended daily adult human dose of laropiprant in two tablets of TREDAPTIVE.

Laropiprant was evaluated in a series of repeated dose toxicity studies of up to 1 year in dogs. In dogs, laropiprant was administered orally at up to 150 mg/kg/day. Consistent increases in serum alanine aminotransferase (ALT) levels were observed in all studies. After 2 and 14 weeks of dosing at 100 mg/kg/day and after 1 year at 25 mg/kg/day, an increase in ALT level was observed. This represents at least 14 times the human exposure based on the AUC of the recommended daily adult human dose of laropiprant in two tablets of TREDAPTIVE. The no-observed-adverse-effect level for the dog studies was 150 mg/kg/day. This represents at least 100 times the human exposure based on the AUC of the recommended daily adult human dose of laropiprant in two tablets of TREDAPTIVE.

Carcinogenicity

Nicotinic Acid

Nicotinic acid was administered to mice for the duration of their life as a 1% solution in drinking water. Mice in this study received approximately 9 to 13 times a human nicotinic acid dose of 2000 mg/day as determined on a mg/m² basis. Nicotinic acid was not carcinogenic under the conditions of this study.

Laropiprant

Laropiprant was not carcinogenic at the highest doses tested in mice and rats.

Laropiprant was evaluated in 2-year carcinogenicity studies in mice and rats at doses of up to 250 mg/kg/day. The no-observed-effect level for neoplastic findings was 250 mg/kg/day. This represents at least 218 to 289 times the human exposure based on the AUC of the recommended daily adult human dose of laropiprant in two tablets of TREDAPTIVE.

Mutagenesis

Nicotinic Acid

Nicotinic acid was not mutagenic in the microbial mutagenicity (Ames) test or in the *in vitro* assay for chromosomal aberrations in Chinese hamster ovary (CHO) cells.

Laropiprant

Laropiprant was not mutagenic or clastogenic in a series of genetic toxicology studies, including the microbial mutagenicity (Ames) test, an *in vitro* rat hepatocyte DNA alkaline elution assay (which measures the compound's ability to induce single strand breaks in

DNA), an *in vitro* assay for chromosomal aberrations in CHO cells, or an *in vivo* micronucleus assay.

Reproduction

Nicotinic Acid

No adverse effects on fertility were observed in male rats given nicotinic acid at oral doses up to 600 mg/kg/day or in female rats given up to 600 mg/kg/day prior to mating and throughout mating. This represents at least 391 times the human AUC of nicotinic acid based on the recommended daily dose of ER nicotinic acid in two tablets of TREDAPTIVE.

Laropiprant

No adverse effects on fertility were observed in male rats given laropiprant at oral doses up to 250 mg/kg/day or in female rats given up to 400 mg/kg/day prior to mating and throughout mating. This represents at least 289 times the human exposure based on the AUC of the recommended daily adult human dose of laropiprant in two tablets of TREDAPTIVE.

Development

Nicotinic Acid

Nicotinic acid was not teratogenic in rats up to doses of 300 mg/kg/day or in rabbits up to doses of 300 mg/kg/day (253 and 104 times the human AUC of nicotinic acid based on the recommended daily dose of ER nicotinic acid in two tablets of TREDAPTIVE). Slight decreases in mean maternal weight gain and foetal body weight, slight decrease in ossification of the sacrocaudal vertebrae, and increased incidence of incomplete ossification of the cervical vertebra, sternebra, and hyoid in the foetus were observed at oral doses of 1000 mg/kg/day in rats (at least 959 times the human AUC of nicotinic acid based on the recommended daily dose of ER nicotinic acid in two tablets of TREDAPTIVE). Similar treatment-related changes were observed at oral doses of 900 mg/kg/day in rabbits (at least 629 times the human AUC of nicotinic acid based on the recommended daily dose of ER nicotinic acid in two tablets of TREDAPTIVE).

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 TREDAPTIVE). Slight decreases in mean maternal weight gain and foetal body weight, slight increases in pup mortality, and increased incidence of supernumerary rib and incomplete ossification of the sternebra in the foetus 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 TREDAPTIVE).

Effects on the Ability to Drive and Use Machinery

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported. (See Adverse Effects.)

Adverse Effects

Clinical Trials Experience

TREDAPTIVE is generally well tolerated. Adverse reactions have usually been mild and transient.

Flushing

Flushing is the most common adverse effect of 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 TREDAPTIVE), flushing was reported by the investigator as a possibly, probably, or definitely medicine-related adverse reaction in 12.3% of patients taking TREDAPTIVE. In these studies, the percentage of patients taking 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 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 TREDAPTIVE (1 g/20 mg per day for Weeks 1-4; 2 g/40 mg per day for Weeks 5-24), ER nicotinic acid (1 g per day for Weeks 1-4; 2 g per day for Weeks 5-24) or placebo (Weeks 1-24). Patients taking TREDAPTIVE experienced significantly less flushing compared to ER 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 TREDAPTIVE to the 2 g/40 mg dose and ER 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 TREDAPTIVE declined and approached that of patients receiving placebo, whereas in patients treated with ER nicotinic acid, the flushing incidence and frequency remained constant (after Week 6). (See Figure 1.)

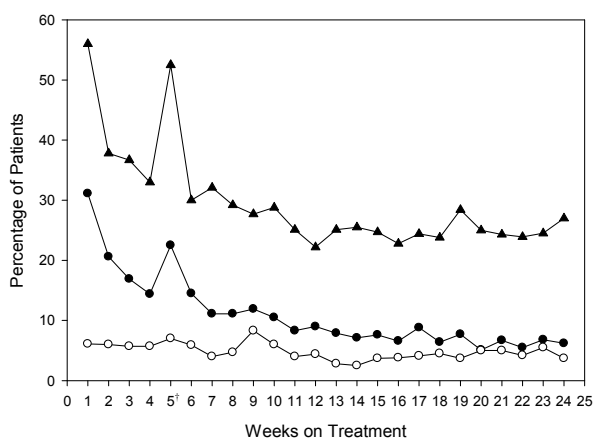
Table 1. Percent of Patients Experiencing Flushing Symptoms with TREDAPTIVE vs. ER Nicotinic acid at Initiation (Week 1)

Treatment Group	Maximum Flushing Symptoms during Initiation (Week 1)			
	None or Mild %	Moderate %	Severe %	Extreme %
ER Nicotinic acid* 1 g (N=529)	44.0	22.7	25.5	7.8
TREDAPTIVE 1 g/20 mg (N=781)	68.9	17.4	10.2	3.5
Placebo (N=262)	93.9	5.7	0.4	0.0

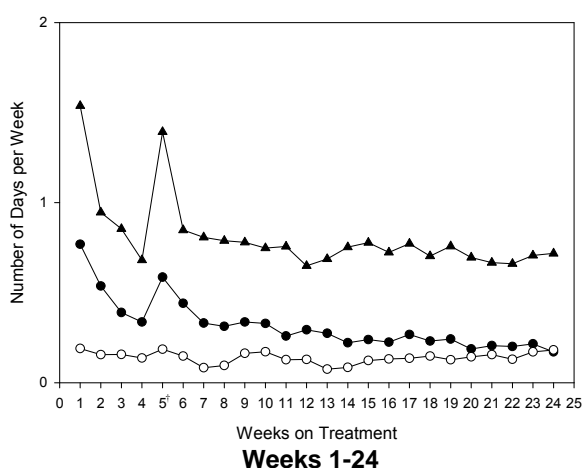
* ER nicotinic acid component of TREDAPTIVE

Figure 1

Panel A. Percentage of Patients with Moderate or Greater* Flushing Symptoms Across Weeks 1-24



Panel B. Average Number of Days per Week with Moderate or Greater* Flushing Symptoms Across Weeks 1-24



● TREDAPTIVE ▲ ER nicotinic acid ○ Placebo

* Includes patients with moderate, severe, or extreme flushing symptoms

† Dose advancement at Week 5

Flushing was also evaluated as a primary endpoint in a 16-week study comparing TREDAPTIVE (one-step dosing regimen of 1 g/20 mg for 4 weeks advanced to 2 g/40 mg for 12 weeks) to nicotinic acid extended-release (manufactured by Kos) (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 TREDAPTIVE experienced significantly fewer days per week with moderate or greater flushing throughout the 16-week study ($p < 0.001$).

Overall Adverse Reactions with TREDAPTIVE

In addition to flushing, the following medicine-related adverse reactions (reported by the investigator as possibly, probably, or definitely medicine-related) were seen in controlled clinical trials in $\geq 1\%$ of patients treated with TREDAPTIVE for up to one year (with or without a statin):

Gastrointestinal disorders: Diarrhoea, 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 ($< 1\%$) characterised by multiple symptoms that may include: angioedema, pruritus, erythema, paresthesia, loss of consciousness, vomiting, urticaria, flushing, dyspnoea, nausea, incontinence of urine and stool, cold sweats, shivering, chills, increased blood pressure, lip swelling, burning sensation, medicine 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) $\geq 3X$ ULN, consecutive) was 1.0% for patients treated with 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 (≥ 10 X ULN) were seen in 0.3% of the patients treated with 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).

Post-marketing Experience and Other Clinical Trial Experience

Additional adverse reactions that have been reported in post-marketing use with TREDAPTIVE or other nicotinic acid products (with or without a statin) or during clinical trials with TREDAPTIVE (<1% of patients) or other nicotinic acid products (with or without a statin) include the following:

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

Eye disorders: Cystoid macular oedema, toxic amblyopia

Gastrointestinal disorders: Abdominal pain, mouth oedema, eructation, peptic ulcer

General disorders and administration site conditions: Asthenia, chills, face oedema, generalised oedema, pain, peripheral oedema

Hepatobiliary disorders: Jaundice

Immune system disorders: Anaphylactic shock, 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: Dyspnoea

Skin and subcutaneous tissue disorders: Acanthosis nigricans, dry skin, hyperpigmentation, macular rash, sweating (night or cold sweat), vesicular or vesiculobullous rash

Vascular disorders: Hypotension, orthostatic hypotension

Interactions

Nicotinic Acid

Effects of Nicotinic acid on Other Medicines

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

HMG-CoA Reductase Inhibitors: (See Warnings and Precautions, *Effect on Skeletal Muscle* and Pharmacokinetics, *Medicine Interactions*.)

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 Medicines on Nicotinic acid

Bile Acid Sequestrants: Because co-administration of bile acid sequestrants may reduce the bioavailability of acidic medicines such as nicotinic acid, it is recommended that 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 (nicotinic acid or nicotinamide) have not been studied with TREDAPTIVE. Physicians should consider the nicotinic acid intake from vitamins and nutritional supplements when prescribing TREDAPTIVE.

Medicine/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 Medicines

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 co-administered with midazolam. (See Pharmacokinetics, *Medicine Interactions*.)

Other Medicines: 1'hydroxymidazolam is metabolised 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 medicines are known to be metabolised predominantly by UGT2B4 or UGT2B7. Although interactions with these medicines are generally <2-fold in magnitude, caution should be used when TREDAPTIVE is co-administered with medicines metabolised predominantly by UGT2B4 or UGT2B7 (e.g., azidothymidine (AZT)). (See Pharmacokinetics, *Medicine Interactions*.)

In medicine interaction 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 medicine

interactions 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.

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 Actions, *Pharmacodynamics; Effects on Platelet Function*).

Aspirin and Clopidogrel: In a clinical study in dyslipidemic patients receiving both aspirin and clopidogrel, laropiprant induced transient (4 hours post-dose) inhibition of platelet function *in vivo* (as evaluated by bleeding time and platelet aggregation studies), but had little effect across the dosing interval. Patients receiving TREDAPTIVE concomitantly with aspirin and clopidogrel should be closely monitored.

Effects of Other Medicines 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.

Overdosage

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 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 Actions, *Pharmacodynamics; Effects on Platelet Function*).

Actions

Mechanism of Action

TREDAPTIVE

TREDAPTIVE contains ER nicotinic acid (nicotinic acid) and laropiprant. The nicotinic acid component of TREDAPTIVE reduces the levels of LDL-C, total cholesterol (TC), very low density lipoprotein-cholesterol (VLDL-C), apo B (the major protein component of LDL and VLDL), TG, and lipoprotein(a) (Lp(a)) and elevates the level of HDL-C and apo A-I (a

major protein component of HDL). Laropiprant suppresses the adverse effect of flushing associated with administration of nicotinic acid.

Nicotinic Acid

The mechanisms by which nicotinic acid modifies the plasma lipid profile are not fully understood. Nicotinic acid inhibits release of free fatty acids (FFA) from adipose tissue and transiently lowers their plasma concentration. The reduced availability of FFA may decrease hepatic FFA uptake and incorporation into TG carried in VLDL, which is accompanied by reduced levels of VLDL-C and apo B. Since LDL is formed by VLDL catabolism, the reduced hepatic VLDL-C output may contribute to the reduced plasma LDL-C and total cholesterol. Additional explanations that do not invoke plasma FFA reduction as the central driver of TG reduction include nicotinic acid-mediated inhibition of either *de novo* lipogenesis or esterification of fatty acids into TG in the liver.

Laropiprant

Flushing associated with nicotinic acid is mediated by release of prostaglandin D2 (PGD₂) in the skin. There are two G-protein-coupled receptor subtypes for PGD₂, DP₁ and DP₂. Genetic and pharmacologic studies in animal models have shown that DP₁, but not DP₂, plays a key role in nicotinic acid-induced vasodilation. Unlike aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) that are known to inhibit the production of multiple prostaglandins, laropiprant is a potent and selective antagonist of DP₁ that inhibits nicotinic acid-induced flushing by specifically blocking the action of PGD₂ on DP₁.

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 hypothesised 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 (niacin) 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 characterised 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 9 α , 11 β -PGF₂, a metabolite of PGD₂, coincided with the onset of flushing. Nicotinic acid does not increase histamine metabolites or the major urinary metabolite of prostaglandin E₂ (PGE₂).

Laropiprant is a potent and selective antagonist of the PGD₂ receptor subtype 1, DP₁, 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 TREDAPTIVE, pre-treatment with aspirin 325 mg had no additional beneficial effects in reducing nicotinic acid-induced flushing symptoms compared to TREDAPTIVE alone. (See Adverse Effects.)

Effects on Platelet Function

Laropiprant is a potent and selective antagonist of the PGD₂ receptor, DP₁. However, it also has affinity for the thromboxane A₂ receptor (TP), although it is approximately 190-fold less potent at TP as compared to DP₁.

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, *Laropiprant*.)

Pharmacokinetics

Absorption

Nicotinic Acid

Following a 2 g dose of ER nicotinic acid administered orally as two tablets of TREDAPTIVE with food, nicotinic acid was absorbed with a median time to peak plasma concentration (T_{max}) of 4 hours, a mean area under the plasma concentration-time curve (AUC_{0-last}) of approximately 58.0 μ M•hr, and a mean peak plasma concentration (C_{max}) of approximately 20.2 μ M. 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 TREDAPTIVE with food, laropiprant was rapidly absorbed with a median T_{max} of 1 hour, a mean AUC_{0- ∞} of approximately 13 μ M•hr, and a mean C_{max} of approximately 1.6 μ M. 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_{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 TREDAPTIVE after an overnight fast.

Distribution

Nicotinic Acid

Nicotinic acid 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 litres. 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 (niacin) 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 metabolised 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 metabolised primarily via acyl glucuronidation, with a smaller component of oxidative metabolism, followed by excretion of the glucuronide into faeces (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 faeces is laropiprant (comprising unabsorbed medicine and/or hydrolysed glucuronic acid conjugate). In urine, the primary medicine-related component is the acyl glucuronide conjugate (64% of radioactivity) with smaller contributions from the parent compound (5%). The oxidative metabolism of laropiprant is catalysed primarily by CYP3A4, whereas several UGT isoforms (1A1, 1A3, 1A9 and 2B7) catalysed 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 faeces (via bile) and urine. Following oral administration of ¹⁴C-laropiprant in humans, approximately 68% of the dose was recovered in faeces (primarily as parent compound, comprising unabsorbed medicine and/or hydrolysed 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 ($t_{1/2}$) following a 40 mg dose of laropiprant administered as two tablets of 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 C_{max} (approximately 1.1-fold).

Characteristics in Patients

Renal Insufficiency

TREDAPTIVE: Use of TREDAPTIVE in patients with renal insufficiency has not been studied.

Nicotinic acid: (See Warnings and Precautions.)

Laropiprant: Administration of laropiprant 40 mg in non-dialysed patients with severe renal insufficiency resulted in no clinically meaningful change in the AUC and C_{max} of laropiprant, compared to healthy control subjects. As no effect was observed in severe renal insufficiency, no effect is expected in patients with mild and moderate renal insufficiency; however, the effects of end-stage renal failure and dialysis on laropiprant pharmacokinetics cannot be inferred from this study.

Hepatic Insufficiency

TREDAPTIVE: Use of TREDAPTIVE in patients with hepatic insufficiency has not been studied.

Nicotinic acid: (See Contraindications and Warnings and Precautions, *Hepatic Effects.*)

Laropiprant: Consistent with the characteristics of a medicine that is primarily cleared by metabolism, moderate hepatic disease has a significant impact on laropiprant pharmacokinetics, with an increase in AUC and C_{max} of approximately 2.8- and 2.2-fold, respectively.

Gender

Nicotinic acid: No dose adjustment is necessary based on gender. Gender has no clinically meaningful effect on pharmacokinetics of ER nicotinic acid. There is no difference in the oral bioavailability of nicotinic acid in men and women receiving TREDAPTIVE. Women have a modest increase in plasma concentrations of nicotinuric acid and nicotinic acid compared to men.

Laropiprant: No dosage adjustment is necessary based on gender. Gender had no clinically meaningful effect on the pharmacokinetics of laropiprant.

Elderly

Nicotinic acid: There is no pharmacokinetic data in the elderly (≥ 65 years). Age has no clinically meaningful effect on pharmacokinetics of ER nicotinic acid based on a composite analysis of subjects ages 18-65 years. There is no change in the oral bioavailability of nicotinic acid with age.

Laropiprant: No dosage adjustment is necessary in the elderly. Age had no clinically meaningful effect on the pharmacokinetics of laropiprant.

Paediatric

TREDAPTIVE: No studies with TREDAPTIVE have been performed in paediatric patients.

Race

Nicotinic acid: No dose adjustment is necessary based on race. Race has no clinically meaningful effect on the pharmacokinetics of ER nicotinic acid based on pharmacokinetic data including subjects of Hispanic, White, Black, and Native American racial groups.

Laropiprant: No dosage adjustment is necessary based on race. Race had no clinically meaningful effect on the pharmacokinetics of laropiprant based on a composite analysis of pharmacokinetic data including subjects of White, Hispanic, Black, Asian, and Native American racial groups.

Medicine Interactions

Nicotinic Acid

Effects of Nicotinic acid on Other Medicines

HMG-CoA Reductase Inhibitors: In pharmacokinetic studies, there was no effect of TREDAPTIVE on the AUC and C_{max} of simvastatin lactone. A modest increase in AUC and C_{max} of simvastatin acid was observed. (See Warnings and Precautions, *Effect on Skeletal Muscle*.) The clinical significance of this increase is unknown.

Laropiprant

Effects of Laropiprant on Other Medicines

Midazolam: Although laropiprant 40 mg 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. (See Interactions.)

Other: Co-administration of laropiprant 40 mg with midazolam increased the $AUC_{0-\infty}$ and C_{max} of 1'hydroxymidazolam, a midazolam metabolite, by 98% and 59%, respectively. 1'hydroxymidazolam is metabolised predominantly by uridine diphosphate-glucuronosyltransferases (UGT) 2B4 and 2B7, which *in vitro* studies have shown are inhibited by laropiprant. These data support the conclusion that laropiprant is a mild to moderate inhibitor of UGT2B4/UGT2B7. (See Interactions.)

Pharmaceutical Precautions

Store below 30°C. Store in the original package until time of use. Protect from light and moisture.

TREDAPTIVE has a shelf life of 24 months when stored as above.

Medicine Classification

Prescription Medicine

Package Quantities

TREDAPTIVE 1 g/20 mg tablets are available in two pack sizes:

- Packs of 28 tablets
- Packs of 56 tablets (not available in New Zealand)

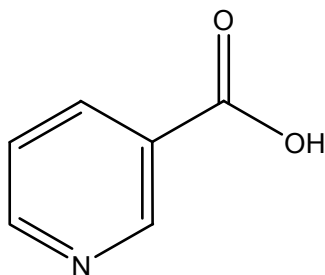
Further Information

Chemistry

TREDAPTIVE contains ER (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.

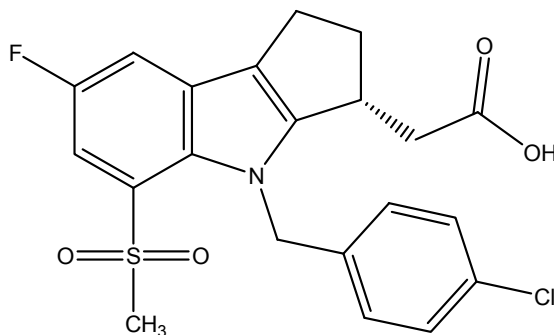
The chemical name of nicotinic acid (or niacin) is 3-pyridinecarboxylic acid. The empirical formula of nicotinic acid is C₆H₅NO₂ and its molecular weight is 123.11.

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



The chemical name of laropiprant is [(3*R*)-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:



Active Ingredients

TREDAPTIVE is available for oral administration as a bi-layer tablet containing 1 g of ER nicotinic acid and 20 mg of immediate-release laropiprant.

Inactive Ingredients

Each bi-layer tablet of TREDAPTIVE contains the following inactive ingredients: hypromellose USP/NF, colloidal silicon dioxide USP/NF, sodium stearyl fumarate USP/NF, hydroxypropyl cellulose USP/NF, microcrystalline cellulose USP/NF, croscarmellose sodium USP/NF, lactose hydrous NF, and magnesium stearate NF.

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