

PRODUCT MONOGRAPH

Pr ADVICOR[®]

extended-release niacin and lovastatin tablets

500/20 mg, 750/20 mg, 1000/20 mg and 1000/40 mg Film-Coated Tablets

Lipid Metabolism Regulator

Manufacturer:
Sepracor Pharmaceuticals, Inc.
Mississauga, Ontario
Canada

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ADVICOR®

extended-release niacin and lovastatin tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	500/20 mg, 750/20 mg, 1000/20 mg and 1000/40 mg Film-Coated Tablets	Hydroxypropyl methylcellulose, povidone, stearic acid, polyethylene glycol, titanium dioxide and polysorbate 80 <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

Therapy with lipid-altering agents should be only one component of multiple risk-factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Medical therapy is indicated as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate.

ADVICOR (extended-release niacin and lovastatin) is indicated for the treatment of primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidaemia (Frederickson Types IIa and IIb) in:

- Patients treated with lovastatin who require further triglyceride (TG) lowering or high-density lipoprotein (HDL)-raising who may benefit from niacin added to their regimen;
- Patients treated with extended-release niacin who require further LDL-lowering who may benefit from having lovastatin added to their regimen.

ADVICOR is not intended for initial therapy (see **DOSAGE AND ADMINISTRATION**). The dose of ADVICOR should be determined by the titration of individual components. The use of ADVICOR should be reserved for patients in whom treatment with lovastatin or NIASPAN® (extended-release niacin) monotherapy has not been adequate to meet treatment goals.

Pediatrics:

No studies in patients under 18 years of age have been conducted with ADVICOR.

CONTRAINDICATIONS

- Pregnant women and lactating mothers (see **WARNINGS AND PRECAUTIONS, boxed Serious Warnings and Precautions**).
- Patients with active liver disease or unexplained persistent elevations in serum transaminases (see **WARNINGS AND PRECAUTIONS**).
- Patients with active peptic ulcer, or active bleeding.
- Patients who are hypersensitive to niacin, lovastatin or to any ingredient in the formulation or component of the container (see **DOSAGE FORMS, COMPOSITION AND PACKAGING**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- ADVICOR preparations should not be substituted for equivalent doses of immediate-release (crystalline) niacin or nicotinic acid. (see **General** section below).
- Cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have substituted sustained-release (modified-release, timed-release) niacin products for immediate-release (crystalline) niacin at equivalent doses (see **Hepatic/Biliary/Pancreatic** section below).
- ADVICOR should be used with caution in patients who consume substantial quantities of alcohol.
- Active liver disease or unexplained transaminase elevations are contraindications to the use of ADVICOR.
- Myopathy (see **Skeletal Muscle** section below).
- Cholesterol and other products of cholesterol biosynthesis pathway are essential components of fetal development, including synthesis of steroids and cell membranes. Because of the ability of lovastatin to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, ADVICOR may cause harm when administered to pregnant women.

ADVICOR should be administered to women of childbearing potential only when such patients practice a reliable form of contraception (see **CONTRAINDICATIONS**).

If the patient becomes pregnant, ADVICOR should be discontinued immediately and the patient should be informed of the potential hazard to the fetus.

Clinically significant warnings and precautions are listed below in alphabetical order.

General

Prior to initiating therapy with ADVICOR, secondary causes for elevation in plasma lipid levels should be excluded (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephritic syndrome, dysproteinemias, obstructive liver disease, and alcoholism) and a lipid profile performed to measure total cholesterol, LDL-C, HDL-C and TG. For patients with TG < 4.52 mmol/L (< 400 mg/dL), LDL-C can be estimated using the following equation:

$$\begin{aligned} \text{LDL-C (mmol)} &= \text{total-C} - [(0.37 \times \text{TG}) + \text{HDL-C}] \\ \text{LDL-C (mg/dL)} &= \text{total-C} - [(0.2 \times \text{TG}) + \text{HDL-C}] \end{aligned}$$

For patients with TG levels > 4.52 mmol/L (> 400 mg/dL), this equation is less accurate and LDL-C concentrations should be measured directly, or by ultracentrifugation.

ADVICOR should not be substituted for equivalent doses of immediate-release (crystalline) niacin or nicotinic acid. For patients switching from immediate-release niacin to NIASPAN, therapy with NIASPAN should be initiated with low doses (i.e., 500 mg once daily at bedtime) and the NIASPAN dose should then be titrated to the desired therapeutic response. Cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have substituted sustained release (modified release, timed release) niacin products for immediate-release (crystalline niacin) at equivalent doses (see **DOSAGE AND ADMINISTRATION**).

Before instituting therapy with a lipid-altering medication, an attempt should be made to control dyslipidaemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see **INDICATIONS AND CLINICAL USE**).

While pretreatment with acetylsalicylic acid (ASA) or other non-steroidal anti-inflammatory drugs (NSAIDs) may reduce flushing of the skin, some patients should not take these medications (e.g., patients who have peptic ulcer or active inflammatory disease of the gastrointestinal system or ASA hypersensitivity; refer to the Product Monograph for the NSAID product).

Niacin:

Elevated uric acid levels have occurred with niacin therapy; therefore, in patients predisposed to gout, niacin therapy should be used with caution. Niacin is rapidly metabolized by the liver, and excreted through the kidneys. ADVICOR is contraindicated in patients with significant or unexplained hepatic dysfunction (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**) and should be used with caution in patients with renal dysfunction.

Lovastatin:

Lovastatin may elevate creatine phosphokinase and transaminase levels (see **WARNINGS AND PRECAUTIONS, Hepatic** and **Skeletal Muscle**, and **ADVERSE REACTIONS**). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Cardiovascular

Data on the safety and efficacy of ADVICOR in patients with unstable angina or in the acute phase of myocardial infarction are not available. Therefore, caution should be used when ADVICOR is administered, particularly when such patients are also receiving vasodilator agents.

Carcinogenesis, Mutagenesis and Fertility Impairment

No studies have been conducted with ADVICOR regarding carcinogenesis, mutagenesis, or impairment of fertility.

Endocrine and Metabolism

Niacin:

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

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

Periodic serum creatine phosphokinase (CK) and potassium determinations should be carried out.

Lovastatin:

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. However, clinical studies have shown that lovastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve, and does not reduce basal testosterone concentration. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown.

Patients treated with lovastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

Gastrointestinal

Patients with a past history of jaundice or peptic ulcer should be observed closely during niacin therapy.

Hematologic

Extended-release niacin tablets have been associated with small, but statistically significant dose-related reductions in platelet count (mean of -11% with 2000 mg). In addition, extended-release niacin tablets have been associated with small but statistically significant increases in prothrombin time (PT) (mean of approximately +4% with 2000 mg); accordingly, patients undergoing surgery should be carefully evaluated. Caution should be observed when ADVICOR

is administered concomitantly with anticoagulants; prothrombin time and platelet counts should be monitored closely in such patients.

It is recommended that in patients taking anticoagulants, PT be determined before starting ADVICOR and frequently enough during early therapy to ensure that no significant alteration of PT occurs. Once a stable PT has been documented, PT can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of ADVICOR is changed, the same procedure should be repeated.

In one long-term study of 106 patients treated with ADVICOR, elevations in prothrombin time (PT) >3 x ULN occurred in 2 patients (2%) during study drug treatment. In a long-term study of 814 patients treated with ADVICOR, 7 patients were noted to have platelet counts <100,000 during study drug treatment. Four of these patients were discontinued, and one patient with a platelet count <100,000 had prolonged bleeding after a tooth extraction. Prior studies have shown that NIASPAN can be associated with dose-related reductions in platelet counts (mean of -11% with 2000 mg) and increases of PT (mean of approximately +4% with 2000 mg). Accordingly, patients undergoing surgery should be carefully evaluated.

Hepatic/Biliary/Pancreatic

No clinical studies have been carried out in patients with impaired liver function.

Patients with a past history of jaundice, hepatobiliary disease, or peptic ulcer should be observed closely during ADVICOR therapy. Frequent monitoring of liver function tests and blood glucose should be performed (see **CONTRAINDICATIONS**). ADVICOR should be used in patients with liver impairment only if the benefits outweigh the risks.

ADVICOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease.

Niacin preparations and lovastatin preparations have been associated with abnormal liver tests. In studies using NIASPAN alone, 0.8% of patients were discontinued for transaminase elevations. In studies using lovastatin alone, 0.2% of patients were discontinued for transaminase levels.

In two double-blind controlled 28-week studies, the 48-week open-label extension of both trials, and one open-label 100-week trial, one percent of patients (10/1145 patients) with normal liver function treated with ADVICOR experienced reversible elevations in AST/ALT to more than 3 times the upper limit of normal (ULN). Three of 10 elevations occurred at doses outside the recommended dosing limit of 2000/40 mg. No patient receiving 1000/20 mg had 3-fold elevations in AST/ALT.

In clinical studies with ADVICOR, elevations in transaminases did not appear to be related to treatment duration. However, elevations in AST and ALT levels did appear to be dose related. Transaminase elevations were reversible upon discontinuation of ADVICOR.

Diabetic patients may experience a dose-related rise in fasting blood sugar (FBS). In clinical studies, which included 1028 patients exposed to ADVICOR (6 to 22% with diabetes type II at baseline), increases in FBS above normal occurred in 46-65% of patients during the study, and 1.4% of patients discontinued treatment. In patients treated with lovastatin or NIASPAN monotherapy, 24 to 41% and 43 to 58% of patients, respectively, had increases in FBS above normal.

Diabetic or potentially diabetic patients should be monitored closely during treatment with ADVICOR, and adjustment of diet and/or hypoglycemic therapy may be necessary.

Renal

No information is available on the safety of ADVICOR in patients with renal insufficiency. ADVICOR should be used with caution in patients with renal dysfunction.

Skeletal Muscle

Lovastatin:

Lovastatin and other inhibitors of HMG-CoA reductase occasionally cause myopathy, which is manifested as muscle pain or weakness associated with grossly elevated creatinine kinase (> 10 times ULN). Rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, has been reported rarely and can occur at any time.

Lovastatin is metabolised by the cytochrome P450 isoform 3A4. Drugs which share this metabolic pathway can raise the plasma level of lovastatin and may increase the risk of myopathy. These include cyclosporin, itraconazole, ketoconazole and other antifungal azoles, the macrolide antibiotics erythromycin and clarithromycin, HIV protease inhibitors, or grapefruit juice.

ADVICOR:

Myopathy and/or rhabdomyolysis have been reported when lovastatin is used in combination with lipid-altering doses (≥ 1 g/day) of niacin. **Physicians contemplating the use of ADVICOR, a combination of lovastatin and extended-release niacin, should 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 month of treatment or during any period of upward dosage titration of either drug.** Periodic CK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent myopathy.

In clinical studies, 1 case of suspected myopathy and no cases of rhabdomyolysis were reported in 1,145 patients treated with ADVICOR at doses up to 2000/40 mg for periods up to 2 years, however, cases of myopathy and rhabdomyolysis have been identified in post-market use of ADVICOR.

Patients starting therapy with ADVICOR should be advised of the risk of myopathy, and told to report promptly unexplained muscle pain, tenderness, or weakness. A CK level above 10 times ULN in a patient with unexplained muscle symptoms indicates myopathy. ADVICOR therapy should be discontinued if myopathy is diagnosed or suspected.

In patients with complicated medical histories predisposing to rhabdomyolysis, such as preexisting renal insufficiency, dose escalation requires caution. Also, as there are no known adverse consequences of brief interruption of therapy, treatment with ADVICOR should be stopped for a few days before elective major surgery and when any major acute medical or surgical condition supervenes. If ADVICOR therapy is discontinued for an extended period, reinstatement of therapy should include a titration period.

The risk of adverse muscle events with statins is dose related and the risk may be increased by concomitant use of statins with other lipid lowering drugs that can cause myopathy when given alone, including niacin. Accordingly, the higher doses of ADVICOR should be reserved for patients who require more aggressive lipid management. It is important that such patients be advised to report as soon as possible symptoms such as muscle ache or weakness. A baseline CK determination is recommended for patients who may require higher doses of ADVICOR.

Use of ADVICOR with other Drugs:

The incidence and severity of myopathy may be increased by concomitant administration of ADVICOR with drugs that can cause myopathy when given alone, such as gemfibrozil and other fibrates. The use of ADVICOR in combination with fibrates should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination. In patients taking concomitant cyclosporine or fibrates, the dose of ADVICOR should generally not exceed 1000/20 mg (see **DOSAGE AND ADMINISTRATION**), as the risk of myopathy may increase at higher doses. Interruption of ADVICOR therapy during a course of treatment with a systemic antifungal azole or a macrolide antibiotic should be considered.

Special Populations

Pregnant Women: ADVICOR is contraindicated in pregnancy. It should be administered to women of childbearing potential only if they practice a reliable method of contraception and have been informed of the potential hazard. Treatment should be immediately discontinued as soon as pregnancy is recognised (see **CONTRAINDICATIONS**).

Niacin - Animal reproduction studies have not been conducted with niacin or ADVICOR. It is also not known whether niacin at doses used for lipid disorders can cause fetal harm when administered to pregnant women or whether it can affect reproductive capacity. If a woman receiving niacin or ADVICOR becomes pregnant, the drug should be discontinued.

Lovastatin - Lovastatin is contraindicated in pregnancy. Lovastatin has been shown to produce fetal skeletal malformations in mice and rats.

Nursing Women: Use of ADVICOR in nursing mothers is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions**).

Pediatrics (< 18 years of age): Safety and effectiveness of ADVICOR therapy in pediatric patients have not been established. No studies in patients under 18 years of age have been conducted with ADVICOR.

Geriatrics (> 65 years of age): No formal studies have been carried out in elderly patients. In controlled and open label studies, the safety and efficacy data in patients over 65 years of age treated with ADVICOR were comparable to data observed in younger patients.

Sex: Data indicate that in patients with primary hypercholesterolemia and dyslipidaemia treated with ADVICOR the changes in lipid concentrations are greater for women than for men.

Monitoring and Laboratory Tests

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most frequently-reported events with ADVICOR (extended-release niacin/lovastatin) are flushing episodes (i.e, warmth, redness, itching and/or tingling), which generally become less common as treatment progresses.

The most frequent adverse events observed in double blind controlled clinical trials were: flushing, infection, headache, pain, diarrhea, nausea and pruritus.

The following potentially serious adverse reactions have been reported in controlled clinical trials: cholecystitis, cholelithiasis and kidney stones.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Clinical studies enrolled 1028 patients; 214 in two controlled trials of 24 weeks duration and 814 in a long term open label study at doses up to 2000/40 mg. Doses were titrated up every 4 weeks up to a maximum of 2000/40 mg.

Controlled Clinical Trials

In two controlled clinical trials, ADVICOR has been evaluated for safety in 214 patients treated for hypercholesterolemia, 65 at doses of 2000/40 mg. Discontinuation due to adverse events occurred in 19% (40/214) of the patients, 18/214 (8%) due to flushing.

The adverse events that occurred at an incidence of 2% or greater are given in the table below.

TABLE 1: Treatment-Emergent Adverse Events in Double Blind Controlled Trials, Irrespective of Causality, Occurring in Frequency of 2% or Greater in Patients Treated with ADVICOR

Adverse Event	ADVICOR	NIASPAN	Lovastatin
Total Number of Patients	214	92	94
Flushing	71%	65%	18%
Body as a Whole	49%	54%	45%
Asthenia	5%	7%	5%
Flu Syndrome	6%	8%	4%
Headache	9%	13%	5%
Infection	20%	15%	20%
Injury, Accidental	3%	4%	4%
Pain	8%	9%	10%
Pain, Abdominal	4%	1%	6%
Pain, Back	5%	5%	5%
Pain, Chest	2%	1%	3%
Cardiovascular System	18%	14%	10%
Hypertension	2%	2%	2%
Digestive System	24%	28%	17%
Diarrhea	6%	9%	2%
Dyspepsia	3%	7%	4%
Flatulence	2%	1%	1%
Gastritis	2%	1%	0
Nausea	7%	12%	2%
Vomiting	3%	5%	0
Hemic and Lymphatic System	3%	1%	3%
Ecchymosis	2%	0	1%
Metabolic and Nutrit. System	17%	13%	14%
CK Increased	2%	1%	2%
Edema, Peripheral	4%	2%	3%
Hyperglycemia	4%	7%	6%
SGOT (AST) Increased	3%	0	1%
SGPT (ALT) Increased	2%	0	1%
Musculoskeletal System	9%	10%	18%
Arthritis	3%	0	3%
Myalgia	3%	5%	9%

Adverse Event	ADVICOR	NIASPAN	Lovastatin
Total Number of Patients	214	92	94
Nervous System	14%	12%	14%
Dizziness	3%	3%	4%
Insomnia	4%	3%	4%
Paresthesia	2%	2%	1%
Respiratory System	12%	15%	11%
Cough Increased	4%	3%	1%
Rhinitis	2%	4%	2%
Sinusitis	4%	1%	2%
Skin and Appendages	18%	21%	12%
Pruritus	7%	8%	3%
Rash	5%	12%	3%
Rash, Maculopapular	2%	0	0
Urticaria	3%	2%	1%
Urogenital System	9%	8%	12%
Infection, Urinary Tract	3%	2%	2%

Less Common Clinical Trial Adverse Drug Reactions

The following adverse events have also been reported with niacin, lovastatin, and/or other HMG-CoA reductase inhibitors, but not necessarily with ADVICOR, either during clinical studies or in routine patient management.

- Body as a Whole: face edema; peripheral chest pain; abdominal pain; generalized edema; chills; malaise
- Cardiovascular: atrial fibrillation; tachycardia; palpitations, and other cardiac arrhythmias; orthostasis; hypotension; syncope
- Eye: toxic amblyopia; cystoid macular edema; ophthalmoplegia; eye irritation
- Gastrointestinal: activation of peptic ulcers and peptic ulceration; dyspepsia; vomiting; anorexia; constipation; eructation; flatulence; pancreatitis; hepatitis; fatty change in liver; jaundice; and rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma
- Metabolic: gout
- Musculoskeletal: muscle cramps; myopathy; rhabdomyolysis; arthralgia; myasthenia
- Nervous: dizziness; insomnia; dry mouth; paresthesia; anxiety; tremor; vertigo; memory loss; peripheral neuropathy; psychic disturbances; dysfunction of certain cranial nerves, leg cramps; nervousness

Skin:	hyper-pigmentation; acanthosis nigricans; urticaria; alopecia; dry skin; sweating; and a variety of skin changes (e.g., nodules, discoloration, dryness of mucous membranes, changes to hair/nails)
Respiratory:	dyspnea; rhinitis
Urogenital:	gynecomastia; loss of libido; erectile dysfunction
Hypersensitivity	An apparent hypersensitivity syndrome has been reported rarely, which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.
Other	migraine

Abnormal Hematologic and Clinical Chemistry Findings

ADVICOR: Elevations in serum transaminases, creatinine kinase and fasting blood glucose, and a reduction in serum phosphorus have been observed.

Niacin: Extended-release niacin tablets have been associated with elevations in lactate dehydrogenase, uric acid, total bilirubin and amylase.

Extended-release niacin tablets have also been associated with reduction in platelet counts and prolongation of prothrombin time.

Lovastatin: Lovastatin has been associated with elevations in alkaline phosphatase, glutamyl transpeptidase and bilirubin, and thyroid function abnormalities (see **WARNINGS AND PRECAUTIONS**).

Open-label, Long-term Clinical Trial

In a 52-week, long-term, open-label study of 814 patients, 550 patients completed one-year of treatment and 454 patients continued into the 48-week extension phase of the trial. Of the 814 patients in the study, 610 received the 2000/40 mg dose and 376 patients remained on study medication for up to 104 weeks (85 - 88 wks at the 2000/40 mg dose). The mean treatment duration for all 814 patients was 66.2 weeks.

Discontinuations due to adverse events occurred in 25% (203/814 patients) during the first year of treatment and in 7% (32/454) during the second year. The most common adverse event that led to discontinuation was flushing (10% during the first year of treatment and 2% during the extension phase).

The adverse events that occurred at an incidence of 2% or greater, irrespective of causality, are given in the table below.

TABLE 2: Treatment-Emergent Adverse Events in Open-label, Long-Term Trial, Irrespective of Causality, Occurring in Frequency of 2% or Greater in Patients Treated in a Long Term Clinical Trial with ADVICOR

Adverse Event	ADVICOR
Total Number of Patients	814
Flushing	65%
Body as a Whole	65%
Allergic reaction	4%
Asthenia	7%
Fever	3%
Flu Syndrome	9%
Headache	13%
Hernia	2%
Infection	28%
Infection, fungal	3%
Injury, Accidental	10%
Pain	21%
Pain, Abdominal	7%
Pain, Back	8%
Pain, Chest	5%
Pain, neck	2%
Cardiovascular System	73%
Angina pectoris	2%
Cardiovascular disease	3%
Hemorrhage	2%
Hypertension	4%
Occlusion, coronary	2%
Palpitation	2%
Vascular disorder	2%
Digestive System	39%
Abscess, periodontal	2%
Anorexia	2%
Colitis	2%
Constipation	5%
Diarrhea	12%
Dyspepsia	9%
Flatulence	5%
Gastrointestinal disorder	3%
Nausea	12%
Vomiting	7%

Adverse Event	ADVICOR
Total Number of Patients	814
Hemic & Lymphatic System	8%
Anemia	2%
Ecchymosis	3%
Metabolic & Nutritional System	26%
Creatine PK increased	5%
Diabetes, mellitus	3%
Edema, peripheral	6%
Glucose tolerance decreased	3%
Hyperglycemia	7%
Hypokalemia	2%
Musculoskeletal System	19%
Arthralgia	2%
Arthritis	3%
Bone disorder	2%
Cramps, leg	4%
Myalgia	5%
Tendon disorder	2%
Nervous System	30%
Anxiety	3%
Depression	3%
Dizziness	7%
Dry mouth	3%
Hypertonia	2%
Insomnia	5%
Paresthesia	5%

Post-Market Adverse Drug Reactions

In an open-label Phase IV study in over 4000 patients at doses of 1000/40 mg for 8 weeks, flushing was the most common adverse event leading to discontinuation of 6% of patients. Incidence of AST/ALT elevations > 3x ULN was 0.24%, increases in CK > 5x ULN occurred in 0.24% of patients and no cases of drug-induced myopathy were observed.

Anaphylactoid reaction, angioedema and thrombocytopenia have been observed during post-marketing use of ADVICOR. Rhabdomyolysis and/or myopathy have also been reported, albeit very rarely, during post-marketing use of ADVICOR. There were no differences in rates when compared with extended-release niacin or lovastatin used as monotherapy.

Cases of erectile dysfunction have been reported in association with the use of statins.

Interstitial lung disease: very rare cases of interstitial lung disease, especially with long term therapy. If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

The following adverse events have been reported with some statins: sleep disturbances, including insomnia and nightmares; mood related disorders including depression.

DRUG INTERACTIONS

Overview

Extended-Release Niacin:

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

Acetylsalicylic acid (ASA): Concomitant administration of ASA may decrease the metabolic clearance of niacin (see **WARNINGS AND PRECAUTIONS, General**).

Bile-Acid Sequestrants: An interval of 4 to 6 hours, or as great an interval as possible, should elapse between the ingestion of bile acid-binding resins and the administration of ADVICOR. An *in vitro* study showed that about 98% of available niacin was bound to colestipol, and 10 to 30% was bound to cholestyramine.

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

Lovastatin:

Serious skeletal muscle disorders, e.g., rhabdomyolysis, have been reported during concomitant therapy of lovastatin or other HMG-CoA reductase inhibitors with cyclosporine, itraconazole, ketoconazole, gemfibrozil, niacin, erythromycin, clarithromycin, nefazodone or HIV protease inhibitors. (See **WARNINGS AND PRECAUTIONS, Skeletal Muscle**).

Coumarin Anticoagulants: Bleeding and/or increased prothrombin time (PT) have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin (see **WARNINGS AND PRECAUTIONS, Hematologic**).

Antipyrine: Lovastatin had no effect on the pharmacokinetics of antipyrine or its metabolites. However, since lovastatin is metabolized by the cytochrome P450 isoform 3A4 enzyme system, this does not preclude an interaction with other drugs metabolized by the same isoform.

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Oral Hypoglycemic Agents: In pharmacokinetic studies of lovastatin in hypercholesterolemic, non-insulin-dependent diabetic patients, there was no drug interaction with glipizide or with chlorpropamide.

Drug-Food Interactions

Concomitant consumption of alcohol or hot drinks may increase the side effects of flushing and pruritus and should be avoided around the time of ADVICOR ingestion.

Drug-Herb Interactions

Interactions with herbal products have not been studied.

Drug-Laboratory Interactions

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

DOSAGE AND ADMINISTRATION

The dosage of ADVICOR (extended-release niacin/lovastatin) must be individualized. The fixed combination is not indicated for initial therapy. The dose of ADVICOR should be determined by titration of individual components (see **Recommended Dose and Dose Adjustment**).

Patients should be placed on a standard cholesterol-lowering diet at least equivalent to the NCEP Adult Treatment Panel III TLC diet before receiving ADVICOR and should continue on this diet during treatment with ADVICOR. If appropriate, a program of weight control and physical exercise should be implemented.

Dosing Considerations

- Equivalent doses of ADVICOR may be substituted for equivalent doses of NIASPAN but should not be substituted for other modified-release (sustained release or time-release) niacin preparations or immediate-release (crystalline) niacin preparations (see **WARNINGS AND PRECAUTIONS**). Patients previously receiving niacin products other than NIASPAN should be started on NIASPAN with the recommended NIASPAN titration schedule, and the dose should subsequently be individualized based on patient response.
- **ADVICOR tablet strengths are not interchangeable.**
- Women may respond at lower ADVICOR doses than men.

- Flushing of the skin may be reduced in frequency or severity by pretreatment with acetylsalicylic acid (see **WARNINGS AND PRECAUTIONS, General**).
- Avoid administration on an empty stomach
- ADVICOR is contraindicated in patients with significant or unexplained hepatic dysfunction.
- No information is available on the safety of ADVICOR in patients with renal insufficiency.
- ADVICOR tablets should be taken whole and should not be broken, crushed, or chewed before swallowing.

Recommended Dose and Dosage Adjustment

ADVICOR should be taken during the evening hours, before or at bedtime, after a low-fat snack. Doses should be individualized according to patient response with the goal being to achieve recommended target lipid levels at the lowest possible dose.

ADVICOR can be substituted if the titrated doses of individual components corresponds to ADVICOR fixed dose combination as shown below in Table 3.

Table 3. Niaspan and Lovastatin Dosing Table

NIASPAN DOSE (mg)	LOVASTATIN DOSE (mg)	CORRESPONDING ADVICOR DOSE (niacin extended release mg/lovastatin mg)
500	20	500/20
750	20	750/20
1000	20	1000/20
1000	40	500/20 (2 tablets) or 1000/40
1500	40	750/20 (2 tablets)
2000	40	1000/20 (2 tablets)

Note: A period of at least 4 weeks is recommended before increasing the dose during titration.

NIASPAN Monotherapy

The tablet strengths of NIASPAN are not interchangeable. Do not alternate between different strengths to provide the same daily dosage. The physician should specify the tablet strengths that the patient should use during titration and continue to use for maintenance therapy.

The recommended starting dose for NIASPAN is 500 mg to be taken at bedtime after a low-fat snack. To reduce the incidence and severity of adverse effects, the dose may be increased after 4 weeks by no more than 500 mg and by 500 mg every 4 weeks thereafter to a maximum of 2000 mg per day, depending on patient response. Patients already receiving a stable dose of NIASPAN may be switched directly to a niacin equivalent dose of ADVICOR (see Table 3).

Lovastatin Monotherapy

The recommended starting dose of lovastatin is 20 mg once daily given with the evening meal. If required, the dose of lovastatin may be increased to a maximum of 40 mg once daily after at least an interval of 4 weeks. Patients already receiving a stable dose of lovastatin, for whom adding NIASPAN is considered appropriate, may receive concomitant dosing with NIASPAN, and switch to ADVICOR once a stable dose of NIASPAN has been reached as recommended for NIASPAN monotherapy above. (see Table 3).

Doses of ADVICOR greater than 2000/40 mg daily are not recommended.

Dosage in Patients with Renal Insufficiency:

Use of ADVICOR in patients with renal insufficiency has not been studied. No information is available regarding the safety of ADVICOR use in patients with renal insufficiency.

Dosage in Patients with Hepatic Insufficiency:

Use of ADVICOR in patients with hepatic insufficiency has not been studied. ADVICOR is contraindicated in patients with significant or unexplained hepatic dysfunction (see **CONTRAINDICATIONS**).

Missed Dose

If a dose of this medication is missed, it is not necessary to make up the missed dose. Skip the missed dose and continue with the next scheduled dose. Do not double doses.

If ADVICOR therapy is discontinued for an extended period (>7 days), reinstatement of therapy should begin with the lowest dose of ADVICOR.

OVERDOSAGE

Supportive measures should be undertaken in the event of an overdose of ADVICOR. Monitor liver function and initiate appropriate therapy if required.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

Lovastatin: Lovastatin is a specific inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate. The conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol. Lovastatin is a prodrug and has little, if any, activity until hydrolyzed to its active

beta-hydroxyacid form, lovastatin acid. The mechanism of the LDL-lowering effect of lovastatin may involve both reduction of VLDL-C concentration and induction of the LDL receptor, leading to reduced production and/or increased catabolism of LDL-C.

Pharmacodynamics

Epidemiologic, clinical and experimental studies have established that high LDL cholesterol (LDL-C), low High Density Lipoprotein cholesterol (HDL-C) and high plasma triglycerides (TG) promote human atherosclerosis and are risk factors for developing cardiovascular disease. Increased levels of HDL-C are associated with decreased cardiovascular risk.

ADVICOR: ADVICOR reduces LDL-C, TC, TG, Lp(a), Apo B, TC:HDL and LDL:HDL, and increases HDL-C and Apo A-1 due to the individual actions of extended-release niacin and lovastatin. The magnitude of individual lipid and lipoprotein responses may be influenced by the severity and type of underlying lipid abnormality.

Niacin: Niacin functions in the body after conversion to nicotinamide adenine dinucleotide (NAD) in the NAD coenzyme system. Niacin (but **not** nicotinamide) in gram doses reduces TC, LDL-C, Apo B, Lp(a) and TG, and increases HDL-C. The magnitude of individual lipid and lipoprotein responses may be influenced by the severity and type of underlying lipid abnormality. The increase in HDL-C is associated with an increase in apolipoprotein A-I (Apo A-I) and a shift in the distribution of HDL subfractions. These shifts include an increase in the HDL₂:HDL₃ ratio, and an elevation in lipoprotein A-I (Lp A-I, an HDL particle containing only Apo A-I). Niacin treatment also decreases serum levels of Apo B, the major protein component of the VLDL and LDL fractions, and of lipoprotein a (Lp(a)), a variant form of LDL independently associated with coronary risk.

In addition, niacin preparations (including extended-release niacin) have been shown to cause favourable transformations in LDL particle size subclass distribution, converting the pattern B phenotype (characterised by a predominance of triglyceride-rich, small dense LDL) to pattern A (characterised by a predominance of large buoyant LDL) or the intermediate AB phenotype. Pattern B LDL phenotype is one manifestation of what has been termed the Atherogenic Lipoprotein Profile (ALP), a Mendelian dominant inherited condition which also includes low levels of HDL-C, raised triglyceride, and insulin resistance.

Lovastatin: Lovastatin has been shown to reduce both normal and elevated LDL-C concentrations. Apo B also falls substantially during treatment with lovastatin. Since each LDL-C particle contains one molecule of Apo B, and since little Apo B is found in other lipoproteins, this strongly suggests that lovastatin does not merely cause cholesterol to be lost from LDL-C, but also reduces the concentration of circulating LDL particles. In addition, lovastatin can slightly increase HDL-C, and modestly reduce VLDL-C and plasma TG.

Pharmacokinetics

Absorption:

ADVICOR: In single-dose studies of ADVICOR, rate and extent of niacin and lovastatin absorption were bioequivalent under fed conditions to that from NIASPAN (extended-release niacin) and lovastatin given alone. After administration of two ADVICOR 1000/20 mg tablets,

approximately 72% of the niacin dose was absorbed as measured by the recovery of niacin and its metabolites in the urine, with peak concentrations of nicotinuric acid in plasma averaging approximately 18 µg/ml and occurring about 5 hours after dosing.

The extent of niacin absorption from ADVICOR was increased by administration with food. The administration of two ADVICOR 1000/20 mg tablets under low-fat or high-fat conditions resulted in a 22 to 30% increase in niacin bioavailability relative to dosing under fasting conditions. Lovastatin bioavailability is affected by food. Lovastatin C_{max} was increased 48% and 21% after a high- and a low-fat meal, respectively, but the lovastatin AUC was decreased 26% and 24% after a high- and a low-fat meal, respectively, compared to those under fasting conditions

Following the administration of a single dose of 1000 mg extended-release niacin and 40 mg lovastatin as the 1000/40 mg ADVICOR tablet formulation versus two 500/20 mg ADVICOR tablets the pharmacokinetic profiles of niacin and its metabolites are different. As a result, ADVICOR tablets of different strengths are not interchangeable.

Lovastatin: Lovastatin appears to be incompletely absorbed after oral administration. Because of extensive hepatic extraction, the amount of lovastatin reaching the systemic circulation as active inhibitors after oral administration is low (<5%) and shows considerable inter-individual variation. Peak concentrations of active and total inhibitors occur within 2 to 4 hours after lovastatin administration.

Lovastatin absorption appears to be increased by at least 30% by grapefruit juice; however, the effect is dependent on the amount of grapefruit juice consumed and the interval between grapefruit juice and lovastatin ingestion.

With a once-a-day dosing regimen, plasma concentrations of total inhibitors over a dosing interval achieved a steady-state between the second and third days of therapy and were about 1.5 times those following a single dose of lovastatin.

Distribution:

Niacin: Niacin is less than 20% bound to serum proteins and distribute into milk. Studies using radiolabeled niacin in mice showed that niacin and its metabolites concentrate in the liver, kidney and adipose tissue.

Lovastatin: Both lovastatin and its beta-hydroxyacid metabolite are highly bound (>95%) to human plasma proteins. Distribution of lovastatin or its metabolites into human milk is unknown; however, lovastatin distributes into milk in rats. In animal studies, lovastatin concentrated in the liver, and crossed the blood-brain and placental barriers.

Metabolism:

Niacin: Niacin undergoes rapid and extensive first-pass metabolism that is dose-rate specific and, at the doses used to treat dyslipidaemia, saturable. In humans, one pathway is through a simple conjugation step with glycine to form nicotinuric acid (NUA). NUA is then excreted, although there may be a small amount of reversible metabolism back to niacin. The other

pathway results in the formation of NAD. It is unclear whether nicotinamide is formed as a precursor to, or following the synthesis of, NAD. Nicotinamide is further metabolized to at least N-methylnicotinamide (MNA) and nicotinamide-N-oxide (NNO). MNA is further metabolized to two other compounds, N-methyl-2-pyridone-5-carboxamide (2PY) and N-methyl-4-pyridone-5-carboxamide (4PY). The formation of 2PY appears to predominate over 4PY in humans.

Lovastatin: Lovastatin undergoes extensive first-pass extraction and metabolism by cytochrome P450 3A4 in the liver, its primary site of action. The major active metabolites present in human plasma are the beta-hydroxyacid of lovastatin (lovastatin acid), its 6'-hydroxy derivative, and two additional metabolites.

Excretion:

ADVICOR: Niacin is primarily excreted in urine mainly as metabolites. After a single dose of ADVICOR, at least 60% of the niacin dose was recovered in urine as unchanged niacin and its metabolites. The plasma half-life for lovastatin was about 4.5 hours in single-dose studies.

Niacin: The plasma half-life for niacin is about 20 to 48 minutes after oral administration and dependent on dose administered. Following multiple oral doses of NIASPAN, up to 12% of the dose was recovered in urine as unchanged niacin depending on dose administered. The ratio of metabolites recovered in the urine was also dependent on the dose administered.

Lovastatin: Lovastatin is excreted in urine and bile, based on studies of lovastatin. Following an oral dose of radiolabeled lovastatin in man, 10% of the dose was excreted in urine and 83% in feces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug.

Special Populations and Conditions

Pediatrics: No studies in patients under 18 years of age have been conducted with ADVICOR.

Geriatrics: In patients who received ADVICOR in double blind and open label studies, responses in LDL-C, HDL-C and TG were similar in younger patients and patients over 65 years of age and older. No overall differences were observed in selected chemistry values between the two groups, except for serum amylase which was higher in older patients.

Sex: Steady-state plasma concentrations of niacin and metabolites after administration of niacin are generally higher in women than in men. Recovery of niacin and metabolites in urine, however, is generally similar for men and women, indicating that absorption is similar for both sexes. Data from the clinical trials suggest that women have a greater hypolipidaemic response than men at equivalent doses of NIASPAN and ADVICOR.

Hepatic Insufficiency: No studies have been performed in patients with hepatic insufficiency (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

Renal Insufficiency: There are no data available on the use of ADVICOR in patients with impaired renal function (see **WARNINGS AND PRECAUTIONS**).

STORAGE AND STABILITY

Temperature:

Store at room temperature (15 to 30°C).

Other:

Keep in a safe place out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ADVICOR is an unscored, capsule-shaped tablet containing 500, 750 or 1000 mg of niacin in an extended-release formulation and 20 or 40 mg of lovastatin in an immediate-release formulation. Tablets are colour-coated with the tablet strength code debossed on one side. ADVICOR 500/20 mg tablets are light yellow and debossed '502' on one side. ADVICOR 750/20 mg tablets are light orange and debossed '752' on one side. ADVICOR 1000/20 mg tablets are dark pink/light purple and debossed '1002' on one side. ADVICOR 1000/40 mg tablets are reddish-brown/brown tablets and debossed '1004' on one side. Tablets are supplied in bottles of 90 tablets. The 500/20 mg tablet strength is also supplied in a 3 tablet blister-pack.

ADVICOR contains the following non-medicinal ingredients: FD&C yellow No 615 (750/20 tablets only), hydroxypropyl methylcellulose, iron oxide yellow (500/20 and 1000/20 tablets only), iron oxide red (500/20, 1000/20 and 1000/40 tablets only), iron oxide black (1000/20 tablets only), macrogol, povidone, polyethylene glycol, polysorbate 80 (500/20, 750/20 and 1000/20 tablets only), stearic acid, and titanium dioxide.

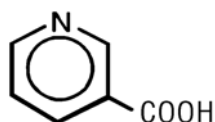
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

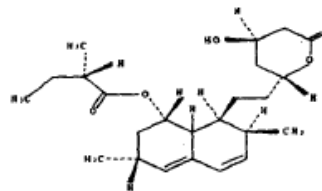
Drug Substance

Proper name:	niacin and lovastatin	
Chemical name:	Niacin:	nicotinic acid or 3-pyridinecarboxylic acid
	Lovastatin:	[1S-[1 (alpha)(R*), 3(alpha), 7 (beta), 8 (beta)]]-1, 2, 3, 7, 8, 8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl) ethyl]-1-naphthalenyl 2-methylbutanoate
Molecular formula and molecular mass:	Niacin:	C ₆ H ₅ NO ₂ , 123.11
	Lovastatin:	C ₂₄ H ₃₆ O ₅ , 404.55
Structural formula:		

Niacin:



Lovastatin:



Physicochemical properties:	Niacin:	White, nonhygroscopic crystalline powder; very soluble in boiling water, boiling ethanol, and propylene glycol; insoluble in ethyl ether. Sparingly soluble in water at 20°C.
	Lovastatin:	White, nonhygroscopic crystalline powder; insoluble in water; sparingly soluble in ethanol, methanol, and acetonitrile.

CLINICAL TRIALS

No mortality and morbidity studies have been conducted with ADVICOR.

Double-Blind Study

In a multi-center, randomized, double-blind, parallel, 28-week, active-comparator study in patients with Type IIa and IIb hyperlipidaemia, ADVICOR was compared to each of its components (NIASPAN and lovastatin). Using a forced dose-escalation study design, patients received each dose for at least 4 weeks. Patients randomized to treatment with ADVICOR initially received 500/20 mg. The dose was increased at 4-week intervals to a maximum of 1000/20 mg in one-half of the patients and 2000/40 mg in the other half. The NIASPAN monotherapy group underwent a similar titration from 500 mg to 2000 mg. The patients randomized to lovastatin monotherapy received 20 mg for 12 weeks titrated to 40 mg for up to 16 weeks. Up to a third of the patients randomized to ADVICOR or NIASPAN discontinued prior to Week 28. ADVICOR decreased LDL-C, TG and Lp(a) and increased HDL-C, see tables 4, 5, 6 and 7 below.

- 1) LDL-lowering with ADVICOR was significantly greater than that achieved with lovastatin 40 mg only after 28 weeks of titration to a dose of 2000 mg/40 mg ($p<.0001$);
- 2) ADVICOR in doses of 1000/20 mg achieved greater LDL-lowering than 1000 mg NIASPAN alone ($p<0.0001$).

The LDL-C results are summarized in Table 4.

TABLE 4: LDL-C Mean Percent Change from Baseline

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

*n = number of patients remaining in the trial at each timepoint

ADVICOR achieved significantly greater HDLC-raising compared to lovastatin and NIASPAN monotherapy at all doses (Table 5).

TABLE 5: HDL-C Mean Percent Change from Baseline

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

*n = number of patients remaining in the trial at each timepoint

In addition, ADVICOR achieved significantly greater TG-lowering at doses of 1000/20 mg or greater compared to lovastatin and NIASPAN monotherapy (Table 6).

TABLE 6: TG Median Percent Change from Baseline

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

*n = number of patients remaining in the trial at each timepoint

The Lp(a) lowering effects of ADVICOR and NIASPAN were similar, and both were superior to lovastatin (Table 7). The independent effect of lowering Lp(a) with NIASPAN or ADVICOR on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

TABLE 7: Lp(a) Median Percent Change from Baseline

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

*n = number of patients remaining in the trial at each timepoint

ADVICOR demonstrated a mean TC:HDL-C change from -27.4% at 500/20 mg to -45.4% at 2000/40 mg. The TC:HDL-C ratio response was significantly greater than the response to lovastatin alone (-28.8%).

DETAILED PHARMACOLOGY

This section details the pharmacology of ADVICOR's individual components, niacin and lovastatin.

Human Pharmacology

Niacin:

Pharmacodynamics: Niacin functions in the body after conversion to NAD in the NAD coenzyme system. Niacin is a potent vasodilator, probably acting directly on vascular smooth muscle of the face and trunk. In gram doses, niacin reduces TC, LDL-C and TG and increases HDL-C. Reductions in VLDL-C and Lp(a) are also seen, and clinical data suggest a favourable effect on the small dense LDL particle phenotype ("pattern B") associated with increased CHD risk. The magnitude of individual effects varies with the underlying hyperlipidaemic condition.

The exact mechanisms by which niacin exerts its effects are not clearly understood, but appear to be diverse. The rates of hepatic synthesis of LDL and VLDL are decreased, for example, as are serum levels of Apo B, while enhanced clearance of VLDL may also occur, possibly due to increased lipoprotein lipase activity. The decreased production of VLDL is thought to result from transient inhibition of lipolysis and from decreases in the delivery of free fatty acids to the liver, in TG synthesis and in VLDL-triglyceride transport. The lowered LDL levels may then result from decreased VLDL production and enhanced hepatic clearance of LDL precursors.

The increase in HDL-C resulting from niacin treatment is associated with a shift in distribution of subfractions, with increases in the proportion of HDL₂ relative to HDL₃ and in Apo A-I respectively. Niacin is not known to affect either the rate of cholesterol synthesis, or the faecal excretion of fats, sterols or bile acids.

Pharmacokinetics: A total of fifteen open-label studies were conducted to investigate the bioavailability and pharmacokinetics of NIASPAN (niacin) (equivalent to extended-release niacin contained in ADVICOR) in humans. Of these, twelve were single-dose, two were multiple dose and one was a dose-rate escalation study.

NIASPAN is well absorbed: approximately 89 to 95% is absorbed relative to immediate-release (IR) niacin based on total urine recovery data. Peak plasma niacin concentrations occur 4 to 5 hours after single- or multiple-dose NIASPAN administration.

The rate of niacin absorption appears to affect the metabolic profile: after single doses, plasma concentrations and urine recovery of niacin and nicotinic acid are higher for IR niacin than for NIASPAN while plasma concentrations and urine recovery of N-methylnicotinamide and N-methyl-2-pyridone-5-carboxamide are lower.

Once-daily administration of NIASPAN in the dose range 1000 mg to 3000 mg for six days resulted in nonlinear accumulation of niacin in plasma. Plasma concentrations of nicotinic acid also accumulated in a nonlinear fashion for NIASPAN 1000 to 2000 mg doses, but nicotinic acid formation appeared to be saturated at the 3000 mg dose, based on dose-corrected AUC comparisons. Plasma N-methylnicotinamide appeared to be dose-proportional in the 1000 to 2000 mg dose range, but plasma data suggested MNA formation became saturated above 2000 mg; dose-corrected C_{max} and AUC decreased with rising niacin dose through 3000 mg.

Niacin and its major metabolites are eliminated in the urine. After single or multiple doses of 1000 mg to 2000 mg NIASPAN, approximately 60 to 75% of the dose is recovered in urine as niacin, nicotinic acid, N-methylnicotinamide and N-methyl-2-pyridone-5-carboxamide. Less than 3% of a single 1500 mg NIASPAN dose is recovered as unchanged niacin in urine. Under steady-state conditions, the proportion of niacin recovered unchanged increases with increasing NIASPAN doses from 1000 to 3000 mg. Steady-state recovery of nicotinic acid increases with increasing NIASPAN doses from 1000 to 2000 mg; the proportion recovered is similar for 2000 and 3000 mg doses. Steady-state recovery of N-methylnicotinamide is relatively consistent across this dose range, while the proportion recovered as N-methyl-2-pyridone-5-carboxamide decreases with increasing NIASPAN dose.

Lovastatin:

Pharmacodynamics: In patients with hypercholesterolemia, lovastatin has been shown to reduce total cholesterol, LDL-C and triglycerides, and increase HDL-C. Maximum therapeutic response can be seen in 4-6 weeks of treatment. The effects of lovastatin induced changes in the lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity and mortality has not been established.

Animal Pharmacology**Niacin:**

Pharmacodynamics: A number of pharmacodynamic studies have been performed using laboratory animal models, demonstrating the effect of niacin on plasma free-fatty acids. In dog studies, reductions were observed in free fatty acid uptake by the hearts of adult dogs, which were intravenously infused with 2.4 mol niacin/ kg body weight/minute for 30 minutes before coronary occlusion and throughout a 15 minute occlusion period. Improvements in myocardial function and subendocardial blood flow were attributed to the effect of niacin on free-fatty acid uptake. A similar experiment was performed using isolated pig hearts *in situ*. A reduction in free-fatty acid accumulation was observed after niacin administration. Cardioprotective effects of niacin were shown by decreased release of creatine kinase, and improved coronary blood flow and cardiac contractility.

The plasma free-fatty acid levels in dogs intravenously dosed with 1 to 32 mg/kg of niacin initially decreased in another study, followed by a rebound elevation to plasma levels greater than baseline, in a dose-related fashion. A similar biphasic effect was seen in rats intravenously dosed at 10 mg/kg. The free-fatty acid rebound mechanism was ascribed to a primary role of the pituitary-adrenal system, since the free-fatty acid rebound in rats was paralleled by an increase in plasma corticosterone levels after niacin administration. A further study showed that niacin blocked the norepinephrine effect on plasma-free fatty acid release in dogs when administered intravenously over one hour at a relatively high dose of 100 mg/kg.

Pharmacokinetics: In a cross-over bioavailability study, beagle dogs were dosed once with 500 mg niacin as the NIASPAN modified-release tablet, once with 500 mg niacin as an oral solution, and once with 187 mg niacin as an iv infusion over three hours. Analysis of plasma for concentrations of niacin and nicotinuric acid were made over suitable time periods (eight hours for the oral doses and four hours for the iv infusion). Nicotinuric acid was found to be a minor metabolite in plasma. The mean plasma niacin C_{max} and T_{max} for 500 mg niacin in NIASPAN were 8.9 $\mu\text{g/mL}$ and 103 minutes, for 500 mg niacin in the oral solution were 86 $\mu\text{g/mL}$ and 37 minutes, and for 187 mg niacin in the iv infusion were 5.3 $\mu\text{g/mL}$ and 103 minutes. The absolute bioavailability of the NIASPAN extended-release formulation was 89%, and absolute bioavailability of the oral solution was approximately 558%, compared to the iv infusion. No adverse effects were observed in the treated dogs from any of the treatment groups.

Metabolism data for laboratory animals from the literature reviewed demonstrate that niacin and nicotinamide are extensively metabolised at levels found endogenously, at therapeutic dose levels (lipid regulating) and higher dose levels. At very high doses, niacin metabolism is saturated.

Lovastatin:

Pharmacodynamics: Lovastatin inhibits cholesterol synthesis *in vitro* in enzyme assays and cell culture assays, and reduces total cholesterol and triglycerides *in vivo*. In animal studies cholesterol reduction was dose dependent during four weeks of treatment.

Pharmacokinetics: Lovastatin is rapidly absorbed after oral administration of DMSO/saline solution or capsule, with about 45% and 23% of the dose absorbed in the rat and dog, respectively.

In rat and dog, lovastatin is rapidly removed from blood, is concentrated in the liver and absorption/excretion tissues, and is rapidly eliminated from the body. In rat, dog, monkey and man, lovastatin is about 95% bound to plasma proteins. Brain uptake was shown to be linear in the rat. No lovastatin was found in aqueous humour or cerebrospinal fluid of dog.

Metabolism has been investigated in mouse, rat and dog. Lovastatin is a lactone which is readily hydrolyzed *in vivo* to the corresponding β -hydroxy acid (lovastatin acid), which is the main active metabolite. The lactone and acid are in equilibrium. Lovastatin undergoes extensive first-pass extraction in the liver and excretion in bile. Thus, little active drug reaches the general circulation. In mouse and rat following intravenous administration of hydroxy acid (HA), the main metabolites in bile were 3'-hydroxy and taurine conjugates. Some 3'-hydroxy-iso-HA and 6'-exomethylene HA were also found in rat. In the dog, following oral administration of lovastatin, the main metabolites in plasma were lovastatin (as the β -hydroxy acid), and the 6'- β -hydroxymethyl, 6'-exomethylene and 6'- β -hydroxyl analogues. Metabolites in bile included 3'-hydroxy-iso-HA. Seven metabolites were found in dog urine, with identical retention times to 7 metabolites found in human urine.

In all species examined, biliary excretion is the major route of elimination, with 78-98% excreted in feces as active and inactivated metabolites following oral administration, and less than 4% excreted in urine as inactive metabolites.

TOXICOLOGY

Niacin: Niacin has been shown to be of low acute toxicity in rats, mice and dogs, when administered via oral and parenteral routes. The LD₅₀ for niacin was 5 to 7 g/kg in rats and mice after oral dosing. Dogs tolerated 2 g/kg without adverse effects. At very high lethal or non-lethal doses, signs of toxicity in rodents included cyanosis, slowed respiration, ataxia and clonic convulsions.

In repeat dose studies with rats and dogs, no signs of toxicity were noted at 1g/kg, and 100 mg/kg per day respectively.

Mice administered daily doses, equivalent to approximately 4.1 g/kg per day for females and 5.4 g/kg per day for male, in their drinking water from six weeks of age throughout the remainder of their lives showed no treatment-related carcinogenic effects and no effects on survival rates.

Female rabbits have been dosed with 0.3 g niacin per day from pre-conception to lactation, and gave birth to offspring without teratogenic effects.

Lovastatin: The acute LD₅₀ by the oral route is greater than 20 g/kg and 5 g/kg in mice and rats, respectively. These doses are vastly in excess of the maximum recommended human therapeutic dose of 80 mg per day.

A marked increase in the lethal and hepatotoxic effects of lovastatin following daily administration of the compound to mice fed on a high cholesterol diet has been reported.

The rabbit was reported to be markedly more sensitive than rodents to the lethal and hepatotoxic effects of lovastatin with mortality occurring within a few days of repeated administration of 100 mg/kg/day. Plasma levels of lovastatin were at least one order of magnitude higher than those in other species although the severity of toxic effects was not related to plasma or hepatic concentrations.

In a multiple dose level study (5, 30, 180 mg/kg/day) in dogs, performed following completion of a nine week pilot study at a single dose level of 180 mg/kg/day, the only notable effect appeared to be a 50% decrease in total serum cholesterol. One high dose (180 mg/kg/day) male died following a tonic convulsion at week 13 of dosing. Histopathological examination showed CNS lesions (vascular degeneration with endothelial hyperplasia, perivascular oedema and multifocal haemorrhage). Optic changes were noted in two other high dose animals (one cataract and one opaque plaque of the posterior capsule).

In mice, hepatic carcinomas and adenomas were seen at 500 mg/kg/day particularly in male animals. A significant increase in the incidence of acanthosis and papillomas in the non-glandular portion of the stomach was seen in both sexes at 500 mg/kg/day. Pulmonary adenomas were also noted in females although the incidence was similar to historical controls.

In rats, a significant increase in hepatic carcinomas was seen in males at 24 months. However, the incidence was similar to that found in controls sacrificed at interim stages of the study and to that observed spontaneously in the same strain of rat.

In both mouse and rat studies the highest doses tested were approximately 300 and 100 times greater respectively than the maximum recommended dose in man on a mg/kg bw basis.

ADVICOR: Based on the results of a 4-week oral toxicity study in dogs dosed by oral gavage, treatment for 28 days at $\geq 900/36$ mg/kg caused emesis, edema of the eyelids, excessive salivation, decreased serum cholesterol and triglyceride levels, and minimal hepatocellular hypertrophy, and in females also a body weight loss. Emesis, edema of the eyelids and decrease in cholesterol level were also seen at 300/12 mg/kg, but with lower incidence and lower severity. The No Observed Effect Level (NOEL) was $<100/4$ mg/kg. The No Observed Adverse Effect Level (NOAEL) was 300/12 mg/kg.

REFERENCES

1. Rubenfire M. Safety and Compliance with Once Daily Niacin Extended-Release/Lovastatin as Initial Therapy in the Impact of Medical Subspecialty on Patient Compliance to Treatment (IMPACT) Study. *Am J Cardiol* 2004;94:306-311.
2. Bays HE *et al.* Comparison of Once-Daily, Niacin Extended-Release/Lovastatin With Standard Doses of Atorvastatin and Simvastatin (The Advicor Versus Other Cholesterol-Modulating Agents Trial Evaluation [ADVOCATE]). *Am J Cardiol* 2003; 91:667-672.

PART III: CONSUMER INFORMATION**ADVICOR®
extended-release niacin and lovastatin tablets**

This leaflet is part III of a three-part “Product Monograph” published when ADVICOR® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ADVICOR. Please read this information carefully before you start taking this medication. It is intended as additional information and does not replace your doctor’s or pharmacist’s advice. Be sure to follow their advice. If you have any questions about ADVICOR, talk to your doctor or pharmacist. Do not decide on your own how to take ADVICOR.

ABOUT THIS MEDICATION**What the medication is used for:**

- ADVICOR is used to improve blood cholesterol levels when the response to an appropriate diet and exercise has been inadequate.
- It is intended for patients treated with lovastatin who require further cholesterol-lowering and who may benefit from niacin added to their regimen or patients treated with niacin who require further cholesterol-lowering who may benefit from having lovastatin added to their regimen.
- You should have been on a cholesterol-lowering diet and exercise program before starting ADVICOR and should continue on this program as directed by your doctor.

This medicine is prescribed for the particular condition you have. Do not give this medicine to other people or use it for any other condition.

What it does:

- ADVICOR lowers Total Cholesterol and specific types of cholesterol such as, LDL-C (bad cholesterol) and triglyceride levels, and increases HDL-C (good cholesterol).

When it should not be used:

- ADVICOR should not be used by pregnant or nursing women.
- ADVICOR should not be used by anyone with allergies (hypersensitivity) to niacin, lovastatin, or any component of this medication or the container (See, “What the nonmedicinal ingredients are:”).
- ADVICOR should not be used by anyone with significant or unexplained liver problems, active stomach ulcers, or active bleeding.

What the medicinal ingredient is:

Extended-release niacin and lovastatin

What the nonmedicinal ingredients are:

FD&C yellow No 615 (750/20 tablet only), hydroxypropyl methylcellulose, iron oxide yellow (500/20 and 1000/20 tablets only), iron oxide red (500/20, 1000/20 and 1000/40 tablets only), iron oxide black (1000/20 tablet only), macrogol, povidone, polyethylene glycol, polysorbate 80 (500/20, 750/20 and 1000/20 tablets only), stearic acid, and titanium dioxide

What dosage forms it comes in:

Film coated tablets of 500/20 mg, 750/20 mg, 1000/20 mg and 1000/40 mg.

WARNINGS AND PRECAUTIONS**Serious Warnings and Precautions**

- **If you become pregnant while using ADVICOR, discontinue use and contact your doctor immediately.**
- **If you are a woman during your child-bearing years, use reliable contraception while taking ADVICOR.**
- **If you were previously taking another niacin (nicotinic acid) (nicotinamide) tablet, your doctor will start you on a lower dose of extended-release niacin tablet (NIASPAN®) and gradually increase the dose before using ADVICOR.**
- **Do not substitute another form of niacin (nicotinic acid) (nicotinamide), used with lovastatin, for ADVICOR without consulting your doctor; improper substitution of niacin can cause severe liver disorders.**
- **Promptly report to your physician any symptoms of muscle pain or weakness, as this may be a sign of a rare, but serious side effect.**
- **Do not consume large quantities of alcohol while taking ADVICOR.**

BEFORE you use ADVICOR talk to your doctor or pharmacist if:

- You are taking any other medications (prescription, non-prescription and natural health products) including other cholesterol lowering medication such as fibrates (gemfibrozil, fenofibrate).
- You have significant or unexplained liver, kidney or thyroid problems, active peptic ulcer, bleeding, diabetes, unstable angina, heart problems, or if you are at risk for low levels of phosphorus in your blood.
- You have a past history of jaundice (yellow skin), liver problems, peptic ulcer, or gout.
- You are pregnant or nursing.
- You have undergone surgery or have had other tissue injury.
- You have a family history of muscular disorders.
- You have had any past problems with muscles (pain, tenderness) after using an HMG-CoA reductase inhibitor (“statin”) such as atorvastatin, fluvastatin, pravastatin,

rosuvastatin or simvastatin or have developed an allergy or intolerance to them.

- You are hypersensitive to niacin, lovastatin or any component of this medication.

INTERACTIONS WITH THIS MEDICATION

Drugs or food that may interact with ADVICOR are listed below. Tell your doctor and pharmacist if you are taking any of these medications.

- cyclosporine
- itraconazole
- ketoconazole
- niacin
- erythromycin
- clarithromycin
- nefazodone or HIV protease inhibitors
- antipyrine
- propranolol
- digoxin
- fibric acid derivatives (bezafibrate, fenofibrate and gemfibrozil)
- oral hypoglycemic agents (drugs which control diabetes)
- vasoactive drugs (drugs which affect blood vessels)
- acetylsalicylic acid
- bile-acid sequestrants (drugs which bind bile acids)
- anticoagulant drugs (drugs which prevent blood clotting) such as warfarin
- alcohol
- hot drinks
- vitamins or other nutritional supplements containing large doses of niacin (greater than 100 mg) or related compounds such as nicotinamide
- grapefruit juice

PROPER USE OF THIS MEDICATION

Usual dose:

ADVICOR is a combination product that supplies a fixed dose of extended-release niacin and lovastatin. Before taking ADVICOR, your doctor will have determined the right dose for you of each component (niacin and lovastatin) and helped you slowly increase your dose of each separately.

ADVICOR is used for maintenance therapy once you have reached a stable dose of niacin and lovastatin.

Doses of ADVICOR greater than 2000/40 mg daily are not recommended. **If ADVICOR therapy is discontinued for an extended period (>7 days), reinstatement of therapy should begin with the lowest dose of ADVICOR.**

ADVICOR tablets are designed to be taken whole. Do not break, crush, or chew them.

Important Note: The tablet strengths of ADVICOR (extended-release niacin/lovastatin) are not interchangeable and you should not alternate between different strengths to provide the same daily dosage. Your doctor will specify the tablet strengths that you should use.

This medication is prescribed for the particular condition you have. Do not give this medication to other people or use it for any other condition.

OTHER HELPFUL HINTS:

- Always take ADVICOR in one dose at bedtime.
- To minimize the risk of stomach upset, take ADVICOR with a low-fat snack.
- Avoid spicy foods and hot or alcoholic beverages around the time of taking ADVICOR.
- **If the side effect flushing is bothersome, (see Side Effects and What to Do About Them, below),** discuss it with your doctor, and your doctor may recommend that you take acetylsalicylic acid, if this is appropriate for you up to 30 minutes before taking ADVICOR. Be sure to tell your doctor about any vitamins or other nutritional supplements containing niacin you are currently taking.

Overdose:

Seek medical attention.

Missed Dose:

You should take ADVICOR every night at bedtime as prescribed. If you miss a dose, take your usual ADVICOR dose the next evening; do not make up for missed doses by taking extra tablets.

If you stop taking ADVICOR for a week or more, contact your doctor for instructions.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

What is flushing?

Niacin sometimes causes redness, warmth, itching, and/or a tingling sensation on the face, neck, chest and back. This is called "flushing". This is a natural reaction signalling that niacin is in the bloodstream.

Most patients on ADVICOR will experience this sensation, usually at the start of therapy or when the dosing is increased. For most patients, the flushing occurs over the first 8 weeks of therapy and will become milder and less frequent as your body adjusts to ADVICOR.

If flushing occurs, it usually does so within 2 to 4 hours after taking ADVICOR and may last for a few hours.

In some patients, flushing may be more intense. Additional symptoms, such as rapid or pronounced heartbeat or dizziness, shortness of breath, sweating, chills, and/or

swelling may occur; on rare occasions, fainting may occur. If the flushing wakes you up and you wish to get out of bed, take your time and get up slowly – especially if you start to feel faint or dizzy, or if you take blood pressure medication.

Other important reactions to be aware of:

- Fever
- Blurred vision
- If you are diabetic, inform your doctor if you notice any changes in your blood sugar.
- You should **inform your doctor immediately and stop taking ADVICOR if you experience any signs of muscle pain, tenderness or weakness as well as generalized weakness and/or brownish or discoloured urine**, as these may be signs of a rare but serious adverse drug reaction.

Other than flushing, the side effects most often seen are gastrointestinal in nature, such as stomach upset, constipation, gas, nausea and diarrhea. Rash, itching, pain in the abdomen, headache and dizziness are also occasionally observed.

Most side effects generally do not require medical attention and may come and go during treatment. But if any effect persists or becomes troublesome, talk with your doctor or pharmacist right away.

Possible side effects reported with some statins:

- breathing problems including persistent cough and/or shortness of breath or fever
- erectile dysfunction
- mood related disorders including depression and sleep disturbances including insomnia and nightmares

IMPORTANT SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Flushing (See “Side effects and what to do about them”)	✓		
Uncommon	Muscle pain, tenderness or weakness		✓	✓

HOW TO STORE IT

Store at room temperature (15 to 30°C).

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345

toll-free fax 866-678-6789

By email: cadrm@hc-sc.gc.ca

By regular mail:

National AR Centre

Marketed Health Products Safety and Effectiveness Information Division

Marketed Health Products Directorate

Tunney’s Pasture, AL 0701C

Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.sepracorpharma.ca>

or by contacting, Sepracor Pharmaceuticals, Inc. at:

1-866-260-6291.

This leaflet was prepared by Sepracor Pharmaceuticals, Inc.

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