

# NEW DRUG UPDATE

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## Advicor® (niacin extended-release and lovastatin)

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### Introduction

Advicor® (niacin extended-release and lovastatin) was approved by the FDA in December 2001. Advicor® is the first cholesterol-lowering combination product for the management of hyperlipidemia. It is indicated for the treatment of primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson Types IIa and IIb) in patients who were previously treated with either niacin extended-release or lovastatin.

### Therapeutic Recommendation

A 28-week study showed that compared to each of its components (niacin extended-release and lovastatin), Advicor® appears to have superior LDL-lowering, HDL-raising, and triglyceride (TG)-lowering effects. After titrating to a 2000 mg/40 mg dose of Advicor®, LDL-lowering was significantly greater than that received with lovastatin 40 mg. Doses of Advicor® 1000 mg/20 mg and higher achieved greater LDL-lowering than niacin extended-release. Advicor® achieved signifi-

cantly higher HDL values compared to lovastatin and niacin extended-release, individually, at all doses. TG reductions were greater in patients treated with Advicor® 1000 mg/20 mg or higher compared to niacin extended-release and lovastatin monotherapy. A 52-week single-arm study of Advicor® found the lipid-altering effects to peak after 4 weeks on the maximum tolerated dose. Alterations were maintained for the duration of the study. Results were similar to findings in the 28-week study. Advicor® decreased LDL 30-42% and TG 32-44% and increased HDL 20-30%. This combination agent provides a convenient dosing formulation when lipid modifications beyond those achieved with monotherapy are required.

### Medication Safety Alert:

**Be careful NOT to confuse Advicor® with Alto-cor® (extended release lovastatin).**

### Dosing and Administration

Advicor® is available in 500 mg/20 mg (light yellow), 750 mg/20 mg (light orange), and 1000 mg/20 mg (dark pink/light purple) unscored, capsule-shaped tablets for oral administration. Advicor® should be taken at bedtime with a low-fat snack. The recommended initial adult dosage for treatment of hypercholesterolemia and mixed dyslipidemia is 500 mg/20 mg at

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bedtime for 4 weeks, then titrated to goal lipid effect as tolerated. The niacin extended-release dose should not be increased by more than 500 mg every 4 weeks to reduce side effects. Doses greater than 2000 mg/40 mg daily are not recommended. If Advicor® therapy is discontinued for more than 7 days, restart at the lowest dose (500 mg/20 mg).

### Cost Comparison

Medication/Dose	Cost <sup>^</sup>		
	Kroger	RiteAid	WalMart
Advicor® (extended release niacin and lovastatin)	52.69	57.99	50.68
Niaspan® (niacin extended release)	32.49	44.99	32.36
Mevacor® (lovastatin)	93.09	87.99	77.72
Lovastatin (generic)	57.59	68.99	57.54

<sup>^</sup>Cost represents price to patient for a 30-day supply of medication at average dosage used.

### Contraindications

Advicor® is contraindicated in patients with known hypersensitivity to niacin, lovastatin, or any component of its formulation, active liver disease or unexplained, persistent elevations in serum transaminases, active peptic ulcer disease, or arterial bleeding.



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### Special Populations

**Pregnancy:** Pregnancy category X. Humans have shown developmental toxicity with lovastatin.

**Lactation:** No studies have been conducted in nursing mothers. Since there is a potential for serious adverse reactions, breast-feeding is not recommended.

**Pediatrics:** There is no evidence to evaluate the safety and effectiveness of Advicor® in patients less than 18 years of age.

**Geriatrics:** Responses to Advicor® were similar in geriatric patients. Amylase was reported to be higher in older patients, but no dosing adjustments are required.

**Hepatic Impairment:** Abnormal liver tests have been reported. Elevations in transaminases appeared to be dose-related, not duration-related. It is recommended to limit the dose to 2000 mg/40 mg. All patients should have liver function tests prior to therapy, then every 6 to 12 weeks for the first 6 months, and at 6 month-intervals thereafter.

**Renal Impairment:** In a study of patients with a creatinine clearance between 10 and 30 mL/min, the plasma concentration after a single dose of lovastatin was about twice that of healthy patients. If creatinine clearance is <30 ml/min doses of lovastatin greater than 20 mg/day are not recommended.

**Gender:** Women have a greater hypolipidemic response to Advicor® than men at equal doses. This is due to gender-specific differences in metabolic rate or volume of distribution. Dosage adjustment is not necessary.

### Drug Interactions

Advicor® is metabolized by the cytochrome P450 isoform 3A4 enzyme and is excreted in the urine. Drugs that inhibit CYP3A4 may increase lovastatin concentrations in the blood, resulting in increased toxicity. Skeletal muscle problems occurred when Advicor® was given with cyclosporine, gemfibrozil, niacin, erythromycin, clarithromycin, nefazodone, HIV protease inhibitors or large quantities of grapefruit juice (>1 quart daily). Systemic azole antifungals (fluconazole, itraconazole, ketoconazole, and miconazole), are contraindicated. These CYP3A4 inhibitors may increase AUC by greater

than 20 times. Since *Monascus purpureus* (Cholestin®) is similar to lovastatin, it should not be used with Advicor®. Separate bile acid sequestrants by at least by 4-6 hours because about 98% of the niacin component was bound to colestipol during drug interaction studies. Avoid vitamins or nutritional supplements that contain large amounts of niacin. This can potentiate adverse effects of Advicor®. A small trial determined that there was no change in prothrombin time (PT) for patients anticoagulated with warfarin. However, bleeding and increased PT have been reported. Advicor® may potentiate the effects of antihypertensive treatment, especially vasodilating agents such as calcium-channel blockers, ganglionic blocking agents, nitrates, adrenergic blocking agents, and other vasodilators, resulting in postural hypotension. Studies show that Advicor® has no pharmacokinetic interaction with antipyrine, propranolol, digoxin, glipizide, or chlorpropamide.

### Adverse Effects

Common adverse drug reactions are flushing episodes (warmth sensation, redness, pruritus, and/or tingling), which occurred in 53-83% of the patients treated with Advicor®. Aspirin has been shown to offset this adverse reaction if administered 30 minutes before the Advicor® dose. Other reactions include hyperglycemia, nausea, diarrhea, dyspepsia, myalgia, headaches, hypotension, elevated creatine kinase and liver transaminases, and hyperuricemia.

### Pharmacology

**Mechanism of Action:** Advicor® contains two antilipemic drugs, niacin extended-release and lovastatin. Niacin (nicotinic acid) is B<sub>3</sub> vitamin, while lovastatin is a hydroxymethylglutaryl CoA (HMG-CoA) reductase inhibitor. Nicotinic acid reduces total serum cholesterol, LDL, VLDL, and triglycerides, and increases HDL cholesterol. Exact mechanism of nicotinic acid is unknown. It may inhibit the release of free fatty acids from adipose tissue, increase lipoprotein lipase activity, decrease triglyceride synthesis, decrease VLDL-triglyceride transport, and/or inhibit lipolysis. The rate of hepatic synthesis of VLDL and LDL is lowered. The HDL elevation is associated with an increase in serum levels of Apo A-I and lipoprotein A-I, and a decrease in serum levels of Apo-B. Lovastatin exerts its effects mainly on total cholesterol and LDL, with minor effects seen on HDL and triglycerides. Lovastatin is a prodrug that

hydrolyzes and competes with HMG-CoA for HMG-CoA reductase. This reduces the amount of mevalonic acid, a precursor of cholesterol, and enhances LDL clearance.

**Absorption/Distribution:** After oral administration of Advicor®, peak niacin concentrations occurred about 5 hours after dosing; about 72% of the niacin dose was absorbed. Less than 20% of niacin is bound to human serum proteins and is distributed into milk. Peak lovastatin concentrations occurred about 2 hours after dosing. Lovastatin and its beta-hydroxyacid metabolite are 95% bound to plasma proteins. Lovastatin crosses the blood-brain barrier and the placental barrier, and may be distributed into human milk. The presence of food increases the absorption of Advicor® by 22-30%.

**Metabolism/Excretion:** Niacin undergoes rapid and extensive first-pass metabolism. Roughly 12% of nicotinic acid is excreted unchanged in the urine with normal doses. Greater proportions of niacin are renally excreted unchanged as dosages exceed 1000 mg/day and metabolic pathways become saturated. Lovastatin metabolized to several other active derivatives by hepatic CYP3A4 isoenzymes. Lovastatin is excreted 10% in the urine and 83% in the feces.

### Patient Information

1. Do not take this medication if you are allergic to niacin or lovastatin.
2. Inform your prescriber if you have an alcohol problem, heart disease, diabetes, infection, muscle problems, low blood pressure, kidney or liver disease.
3. Advicor® should be taken at bedtime with a low-fat snack.
4. Swallow the tablet with a drink of water. Do not take Advicor® with grapefruit juice and do not drink hot drinks or alcohol around the same time.
5. Skin flushing (warmth, redness, itching, tingling and/or burning) is the most common adverse reaction.
6. If skin flushing becomes a problem, ask your health care provider if you can take aspirin before Advicor® doses. Taking one dose of aspirin 30 minutes before Advicor® can help to decrease the amount of flushing you experience.
7. Until you know how niacin affects you, do not drive, use machinery, or do anything that needs

- mental alertness. To avoid dizzy or fainting spells, do not stand or sit up quickly.
8. Tell your prescriber as soon as you can if you get any unexplained muscle pain, tenderness, or weakness, especially if you also have a fever, dark urine, or are abnormally tired.
  9. You will need to have regular tests to make sure your liver is working properly.
  10. Some medications are unsafe to use while you are taking Advicor®. Always tell your doctor about everything you are taking including prescription medications, over-the-counter products, vitamins, and herbals.
  11. Advicor® is only part of a total cholesterol-lowering program. Your physician or dietician can suggest a low-cholesterol and low-fat diet that will reduce your risk of getting heart and blood vessel disease. Avoid alcohol and smoking, and keep a proper physical activity schedule.
  12. You may notice the empty shell of the tablet in your stool; this is no cause for concern.

**References**

1. Advicor® prescribing information. Kos Pharmaceuticals, Inc., Miami, FL, Sept 2002
2. Gupta EK, Ito MK. Lovastatin and extended release niacin combination product: the first drug combination for the management of hyperlipidemia. *Heart Disease* 2002; 4(2):124-37
3. Scarpa WJ. Advicor® (niacin extended-release and lovastatin tablets). *J Clinical Hypertension* 2002; 4(2):146

**Elidel® (pimecrolimus)**

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**Introduction**

Elidel® (pimecrolimus) is a new topical cream approved by the FDA in December 2001 for the treatment of mild to moderate atopic dermatitis in non-immunocompromised patients ages two and older who 1) are not responsive to conventional therapy 2) are intolerant of conventional therapy or 3) are deemed ineligible for conventional therapies.

**Therapeutic Recommendation**

**Elidel® (pimecrolimus) 1% cream is used in the**

**treatment of mild to moderate atopic dermatitis. Medication interactions are not expected due to the limited systemic absorption of pimecrolimus; however, drug interactions (immunizations included) have not been evaluated. Although the use of pimecrolimus is indicated for ages 2 and older, the manufacturer does not recommend pediatric use. Pimecrolimus has been shown to have less dermatological reactions upon application than Protopic® (tacrolimus) topical ointment. Tacrolimus reports the incidence of skin burning to be 43%-58% and pruritus to be 41%-46%. The incidence of these events with pimecrolimus was reported to be 25.9% and 5.5% respectively. Neither tacrolimus nor pimecrolimus produce the epidermal atrophy or striae distensae that have been reported with glucocorticoid therapy. Furthermore, the immunosuppressive effect of pimecrolimus was found to be to be lower than that of tacrolimus.**

**Dosing and Administration**

Pimecrolimus should be thinly applied twice daily to the affected area and gently/completely rubbed into the skin. All skin surfaces, including the head, neck, and intertriginous areas are eligible application sites. Pimecrolimus may be used for the duration of persistent signs and symptoms of atopic dermatitis. Discontinuation of use is desired upon disease resolution. Re-evaluation is necessary for those patients with symptoms persisting beyond six weeks.

**Cost Comparison**

Medication/Dose	Cost <sup>^</sup>		
	Kroger	Kmart	RiteAid
Elidel® (pimecrolimus)			
15 gm	33.09	32.97	30.99
30 gm	57.29	56.97	61.99
100 gm	173.49	151.97	192.99
Protopic® (tacrolimus)			
0.03% 30 gm	72.39	65.97	69.99
0.03% 60 gm	143.59	121.97	139.99
0.1% 30 gm	77.29	69.97	73.99
0.1% 60 gm	153.99	130.97	147.99

**Contraindications**

The use of pimecrolimus is contraindicated in patients with a hypersensitivity to pimecrolimus or any cream component.

## Precautions

1. Do not apply to areas of active cutaneous viral infection.
2. Treatment with pimecrolimus may be associated with an increased risk of varicella zoster infection and herpes simplex virus infection.
3. 14 cases of lymphadenopathy have been reported with pimecrolimus use.
4. 15 cases of skin papilloma or warts were observed with pimecrolimus use.
5. Skin tumor formation in animal photo-carcinogenicity was hastened with the use of pimecrolimus cream.
6. Patients must minimize/avoid natural or artificial sunlight exposure.
7. The systemic absorption of pimecrolimus is increased in patients with Netherton's Syndrome (an inherited autosomal recessive genodermatosis).
8. Use of pimecrolimus in immunocompromised patients is not supported.
9. Localized symptoms are most common during the first few days of application. Most application site reactions lasted no more than five days and were mild to moderate in severity.

## Special Populations

**Pediatrics:** Use is not recommended. Blood concentrations in adults with atopic dermatitis were found to be comparable with concentrations in children. However, no correlation between amount of cream, degree of BSA involvement, and blood concentrations could be found. A higher incidence of upper respiratory symptoms/infections was seen in children as compared to adults.

**Pregnancy:** Pregnancy category C. There have been no adequate, well-controlled studies administering pimecrolimus in this population. Animal testing has revealed no maternal toxicity, embryotoxicity, or teratogenicity; trans-placental crossing was observed. This medication should only be used during pregnancy if clearly needed.

**Lactation:** It is not known whether pimecrolimus is excreted in human milk. If the medication is clearly needed, a decision must be made concerning whether to discontinue nursing or discontinue medication.

**Geriatric:** This population was not specifically addressed in safety and efficacy trials.

**Renal Insufficiency and Hepatic Insufficiency:** No dosage change is required in renal insufficiency due to the low systemic exposure of pimecrolimus.

## Drug Interactions

Interactions between pimecrolimus and other medications (including immunizations) have not been evaluated. Systemic interactions are not expected due to the very low blood levels of pimecrolimus after topical application.

## Adverse Effects

In placebo-controlled studies, pimecrolimus cream did not induce photoallergy, phototoxicity, or contact sensitization. Overall, an increased incidence of urticaria, skin infection, superinfection, rhinitis, and impetigo was found in the pimecrolimus group versus vehicle. Three percent of the vehicle treated patients and four percent of the pimecrolimus treated patients discontinued therapy due to adverse events such as application site reactions and cutaneous infections. The most common application site reaction was burning.

**Children (ages 2 to 17):** Nasopharyngitis (26.5%), headache (25.4%), cough (15.8%), influenza (13.2%), pyrexia (12.5%), application site burning (8.5%), sore throat (8.1%), diarrhea (7.7%), vomiting (6.6%), upper respiratory tract infections (4.8%), rhinitis (4.4%), nausea (4%), constipation (3.7%), conjunctivitis (2.2%), skin infections (2.2%), application site pruritis (1.8%), acne (1.5%)

**Adults:** Application site burning (25.9%), influenza (9.8%), nasopharyngitis (7.6%), headache (7%), application site irritation (6.4%), skin infection (6.4%), folliculitis (6.1%), application site pruritis (5.5%), upper respiratory tract infection (4.3%), sore throat (3.7%), conjunctivitis (3%), cough (2.4%), rhinitis (2.1%), diarrhea (2.1%), acne (1.8%).

## Pharmacology

**Mechanism of Action:** Although the exact mechanism of action for pimecrolimus is unknown, the following have been observed: inhibition of T cell activation, inhibition of the release of mast cell inflammatory cytokines and mediators, and inhibition of the calcium-dependent phosphatase (calcineurin). Pimecrolimus was shown to directly

and specifically affect pro-inflammatory mediator release from mast cells and histamine release from basophils.

**Absorption/Distribution:** Pimecrolimus' systemic absorption is very low. Blood pimecrolimus concentrations are usually at or below the assay's limit of quantification (<0.5 ng/mL). No evidence of drug accumulation was present in patients with detectable blood levels. The plasma protein binding of pimecrolimus was found to be 74%-87%.

**Metabolism/Excretion:** Studies in human liver indicate that pimecrolimus is metabolized via the CYP3A4 enzyme. No evidence of skin metabolism was found. 78.4% of pimecrolimus is eliminated in the feces as metabolites; less than 1% of pimecrolimus was recovered unchanged.

### References

1. Elidel® prescribing information. Novartis Pharmaceuticals Inc. East Hanover, NJ. December 2001.
2. Protopic® prescribing information. Fujisawa Healthcare, Inc. Deerfield, IL. December 2000.
3. Torsten, et. al. "The ascomycin macrolactam pimecrolimus (Elidel, SDZ ASM 981) is a potent inhibitor of mediator release from human dermal mast cells and peripheral blood basophils." *J Allergy Clin Immunol* 2001;108:275-80.

### Patient Information

1. For external use only.
2. You and/or your caregivers should wash hands after application if the hand(s) are not the area for treatment.
3. Avoid natural and artificial sunlight (tanning beds or UVA/B treatment) while using pimecrolimus cream.
4. Do not use pimecrolimus for any other disorder other than for which it was prescribed.
5. Discontinue pimecrolimus use after signs and symptoms of atopic dermatitis have resolved.
6. Report any signs or symptoms of adverse reactions to your prescriber.
7. You may experience application site reactions such as a mild to moderate feeling of warmth and/or a sensation of burning. If the reaction is severe or persists for more than 1 week, contact your physician.
8. If there is no improvement in the atopic dermatitis after six weeks of treatment, or, if at any time, the condition worsens, contact your physician.



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