

Monograph

POLICOSANOL

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I. DESCRIPTION

Policosanol is a proprietary product containing a natural mixture of higher aliphatic primary alcohols isolated and purified from the wax of sugar cane (*Saccharum officinarum*, L.). The components of policosanol include 1-octacosanol, 1-dotriacontanol, 1-triacontanol, 1-tetracosanol, 1-tetratriacontanol, 1-hexacosanol, 1-heptacosanol and 1-nonacosanol. Each coated Policosanol tablet contains 6 mg policosanol. The relative composition of each policosanol component in these products is standardized within a narrow range from batch to batch and is stable under storage conditions.

II. INDICATIONS

Policosanol is indicated as an adjunct to dietary and lifestyle recommendations to reduce elevated LDL-C and total cholesterol levels. Its primary application is in type II hypercholesterolemia including IIa subtype (characterized by elevated total serum cholesterol and LDL-C levels) and IIb subtype (mixed hypercholesterolemia characterized by elevated total serum cholesterol, LDL-C and triglyceride levels). Policosanol can also be used as an alternative to aspirin as an anti-platelet agent.

Table 1. General endpoints for cholesterol management in atherosclerosis

	Primary Prevention (absence of clinical signs/symptoms)	Secondary prevention (presence of clinical signs/symptoms)
Total cholesterol	<200 mg/dl (5.2 mmol/l)	LDL-C must be determined
LDL-C	<130 mg/dl (3.4 mmol/L)	<100 mg/dl (2.6 mmol/l)

III. DOSAGE

The recommended starting dose is 10 mg once a day with the evening meal, since cholesterol biosynthesis is increased at night. If the response is not adequate after an interval of at least 2 months, the dose can be doubled to the maximum recommended dosage of 20 mg/day.

IV. PHARMACOKINETICS

Policosanol is rapidly absorbed based on radioactive absorption studies in experimental animals (rats, rabbits and monkeys) and humans.^{1,2} Peak levels have been achieved from 30 to 120 min after treatment in different animal species and humans. Radioactivity is mainly distributed in the liver while radioactivity levels in the systemic circulation are low. This effect is an advantage for a cholesterol-lowering agent since the liver is the main organ for synthesis and regulation of cholesterol metabolism. Excretion studies in animals and human healthy volunteers have demonstrated that feces is the main route for radioactivity excretion after oral administration, urinary excretion is not relevant.

V. EXPERIMENTAL PHARMACOLOGY

The pharmacological effects of policosanol based on experimental models can be summarized as follows:

· Policosanol produces a dose-dependent and significant reduction of serum total cholesterol and LDL-C levels. HDL-C values were also increased in a dose-dependent manner. Triglycerides are also significantly reduced, but the reduction is not dose-dependent.^{3,4}

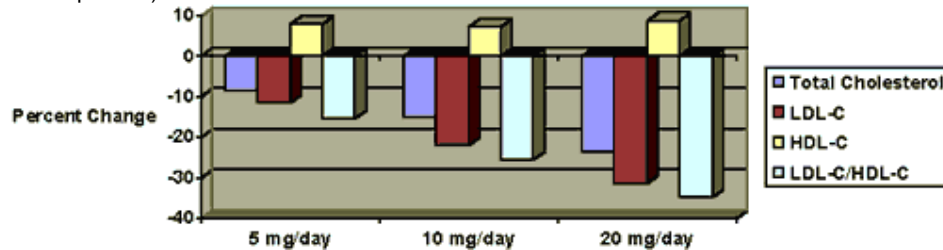
- Policosanol lowers total and LDL-C by:
 - Inhibiting cholesterol synthesis at a point between the formation of acetate and mevalonate.^{5,6}
 - Exerting no direct inhibition on HMG-CoA reductase.^{5,6}

- Significantly increasing LDL receptor dependent processing as demonstrated by increasing the incorporation of LDL into the hepatocyte and stimulating its catabolism.^{5,6}
- Policosanol not only effectively decreases serum cholesterol levels, but also reduces the cholesterol content in different tissues such as liver, heart and fatty tissue.⁷
- The cholesterol-lowering effects of policosanol are persistent and it does not lose its effect over time.
- Policosanol reduces platelet aggregation by altering prostaglandin synthesis. Specifically, policosanol lowers serum levels of the pro-aggregatory thromboxane A₂, while increasing the anti-aggregatory prostaglandin prostacyclin.⁸⁻¹⁰
- Policosanol prevents and reverses atherosclerotic lesions and thrombosis.¹¹⁻¹⁵
- Policosanol prevents intimal thickening and smooth muscle cell proliferation.^{16,17}
- Policosanol is an effective antioxidant in preventing LDL oxidation.^{18,19}

VI. CLINICAL EFFICACY

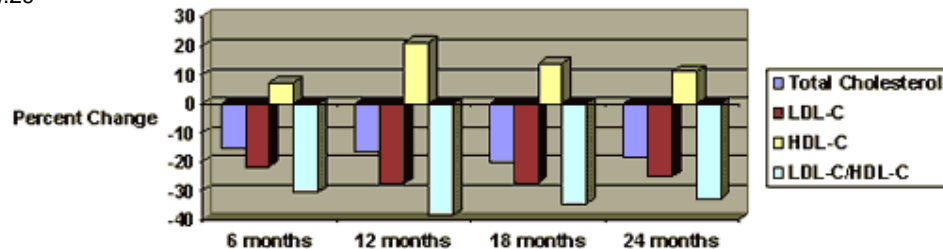
Policosanol is a new cholesterol-lowering agent, with exceptional clinical documentation demonstrating efficacy, safety and tolerability in patients with type II hypercholesterolemia and in patients with secondary hypercholesterolemia associated to diabetes mellitus or nephrotic syndrome. The clinical studies have included short and long-term, randomized, placebo-controlled and comparative studies versus statins (lovastatin, pravastatin and simvastatin), fibrates (bezafibrate and gemfibrozil), acipimox, and probucol involving nearly 3,000 subjects. In these studies, policosanol in dosages ranging from 5 to 20 mg/day, has demonstrated significant improvements in LDL-C, total cholesterol, HDL-C, and the ratios of total cholesterol to HDL-C and LDL-C to HDL-C. Policosanol produces cholesterol-lowering effects within the first 6-8 weeks of use. At a daily dosage of 10 mg of policosanol at night, LDL cholesterol levels typically drop by 20 to 25% within the first six months of therapy. At a dosage of 20 mg, LDL levels typically drop by 25-30%. HDL cholesterol levels typically increase by 15 to 25% after only two months of use. The combined LDL reduction and HDL increase can produce dramatic improvements in the LDL to HDL ratio.

Figure 1. The lipid-lowering effects of policosanol are dose-dependent (% changes compared to placebo in eight-week treatment periods).²²



These improvements in lipid profiles compare quite favorably to results observed with statin drugs. From comparative studies it can be concluded that 10 mg of policosanol is equivalent in efficacy to 20 mg of lovastatin, 10 mg pravastatin, and 10 mg of simvastatin. But, while these drugs have well-known side effects, policosanol is completely safe. Policosanol has not been shown to produce any adverse drug interaction as well and it can be used in diabetics, elderly subjects, and even in patients with impaired liver function or severe liver damage without fear of side effect. In addition to its effects on cholesterol levels, policosanol also exerts additional positive effects in the battle against atherosclerosis. It prevents excessive platelet aggregation without effecting coagulation, prevents smooth muscle cell proliferation into the intima of the artery, and exerts good antioxidant effects in preventing against LDL oxidation. The recommended dosage of policosanol is 10 mg at the evening meal. It is given at night because most cholesterol manufacture occurs at night. As with other cholesterol-lowering therapies, dosage can be adjusted based upon checking the blood cholesterol levels every 8 weeks or so.

Figure 2. The efficacy of 10 mg of policosanol daily is maintained in long-term therapy (comparison vs. placebo).²⁹



VII. DOUBLE-BLIND STUDIES VS. CHOLESTEROL-LOWERING DRUGS

Policosanol has been compared with statin drugs (lovastatin, simvastatin and pravastatin) fibrates (gemfibrozil), acipimox, and probucol in randomized, double blind, short-term clinical trials conducted in patients with type-II hypercholesterolemia.

Vs. Lovastatin

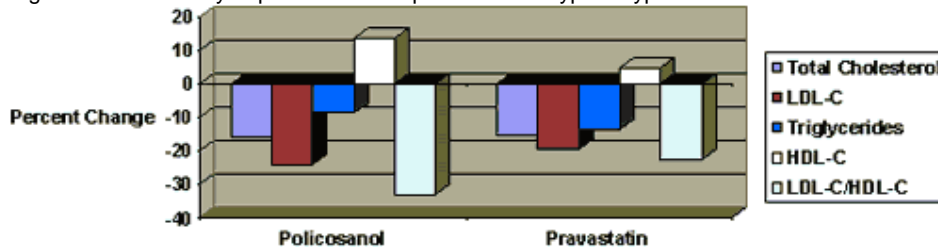
Policosanol administered for eight weeks at 10 mg day has shown a similar efficacy to lovastatin administered at

20 mg/day.^{31,32} Both drugs produced similar decreases in LDL-C levels, while lovastatin was slightly more effective than policosanol in reducing total cholesterol. However, the reason is that policosanol, but not lovastatin, significantly increased HDL-C levels in these studies. Policosanol raised HDL levels by over 17% from baseline values while lovastatin actually decreased HDL-C levels slightly. Another advantage for policosanol is that it has no hepatotoxic effect. Lovastatin significantly, but moderately, increased serum transaminases and creatine phosphokinase values while policosanol did not. Other side effects were also more frequent in lovastatin-treated patients.

Vs. Pravastatin

Policosanol administered at 10 mg/day was compared with the same dosage of pravastatin for eight weeks.³³ The policosanol group demonstrated greater percent changes of LDL-C and HDL-C than the pravastatin group. Side effects were more frequent in the pravastatin group than in policosanol group. While pravastatin produced a significant increase the serum levels of alanine and aspartate aminotransferase (ALT and AST, respectively), policosanol exhibited no hepatotoxicity.

Figure 3. The efficacy of policosanol vs. pravastatin in type II hypercholesterolemia.³³



Vs. Simvastatin

Policosanol and simvastatin were found to be equally effective at dosages of 10 mg/day for eight weeks in patients with type-II hypercholesterolemia.^{34,35} In patients with type-II hypercholesterolemia and concomitant NIDDM, policosanol, but not simvastatin, significantly increased HDL-C levels.³⁵ Again, more adverse experiences were and have been reported in simvastatin treated patients than in policosanol treated patients.

Vs. Fibrates

Different studies have compared the effects of policosanol and fibrates, such as gemfibrozil and bezafibrate.³⁶⁻³⁸ The results have shown that policosanol produces slightly higher reductions of serum total cholesterol, LDL-C, ApoB and the atherogenic ratios of cholesterol to HDL-C and LDL-C to HDL-C, while the fibrates have reduced triglycerides more effectively. Similar results were seen in increasing HDL-C levels. However, like the statin drugs, fibrates, but not policosanol, have increased serum transaminase levels and the adverse experiences reported by fibrates-treated patients have been more frequent than policosanol-treated patients.

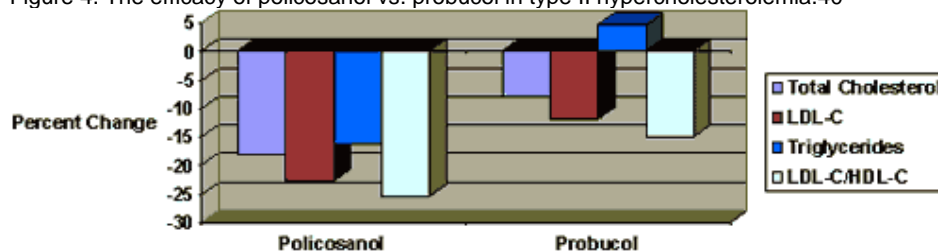
Vs. Acipimox

A comparative double blind clinical trial versus acipimox for eight weeks in type II hypercholesterolemic patients has shown that policosanol is more effective than acipimox in reducing LDL-C and total cholesterol.³⁹ In addition, serum Lp(a) levels were significantly reduced by policosanol treatment both in the whole study population (32.6 % reduction) as well as in the stratum showing initial high Lp(a) levels (> 30 mg/dl) (57.4 % reduction). Lp(a) is a plasma lipoprotein with a structure and composition that closely resembles LDL, but with an additional molecule of an adhesive protein called apolipoprotein (a). Elevated plasma levels of Lp(a) are an independent risk factor for coronary heart disease, particularly in patients with elevated LDL cholesterol levels. In fact, a high level of Lp(a) has been shown to carry a ten times greater risk for heart disease than an elevated LDL cholesterol level. That is because LDL on its own lacks the adhesive apolipoprotein (a). As a result, LDL does not easily stick to the walls of the artery. Levels of Lp(a) below 20 mg/dl are associated with a low risk for heart disease; levels between 20 and 40 mg/dl a moderate risk; and levels above 40 mg/dl an extremely high risk for heart disease.

Vs. Probucol

A comparative study of policosanol (10 mg/day) vs. probucol (1,000 mg/day) for eight weeks in patients with type-II hypercholesterolemia showed that policosanol was more effective in reducing LDL-C and total cholesterol than probucol.⁴⁰ Both drugs were safe and well tolerated.

Figure 4. The efficacy of policosanol vs. probucol in type II hypercholesterolemia.⁴⁰



VIII. DOUBLE-BLIND TRIALS IN SPECIAL POPULATIONS

Policosanol in Diabetics

Policosanol administered to non-insulin dependent diabetes mellitus (NIDDM) patients with type-II hypercholesterolemia significantly lowered LDL-C, serum total cholesterol and atherogenic ratios, while

increasing HDL-C levels. In addition, policosanol does not impair glycemic control in diabetic patients as assessed through the evaluation of its effects on blood glucose and glycosylated hemoglobin (HgbA1c) values.^{41,42}

Table 2. Effect of policosanol on serum lipid profile of patients with NIDDM.⁴¹			
<i>Treatment</i>	<i>Baseline</i>	<i>12 weeks</i>	<i>Percent change</i>
Total cholesterol (mmol/L)			
Policosanol	7.51	5.35	-28.9
Placebo	7.94	8.01	+0.4
LDL-C (mmol/L)			
Policosanol	5.27	3.05	-44.4
Placebo	5.32	5.56	+3.4
HDL-C (mmol/L)			
Policosanol	1.47	1.58	+23.5
Placebo	1.51	1.52	+0.7
Triglycerides (mmol/L)			
Policosanol	2.06	1.96	-2.4
Placebo	2.45	2.11	+6.5
Total cholesterol to HDL-C			
Policosanol	5.88	3.52	-38.3
Placebo	5.72	6.03	+3.8
LDL-C to HDL-C			
Policosanol	4.25	2.01	-51.6
Placebo	3.99	4.16	+2.9

Policosanol in Hypertensives

Policosanol significantly reduced LDL-C (-19.1%), total cholesterol (-13%) and the ratios of cholesterol to HDL-C (-20%) and LDL-C to HDL-C (-24.2%) in hypertensive patients with hypercholesterolemia, while significantly increasing HDL-C levels (+17.1%).⁴³ After 12 months of therapy policosanol significantly lowered systolic pressure (-10 mm Hg), while in the placebo group the values remained unchanged. Many of the patients were on beta-blockers and diuretics, two classes of drugs known to adversely impact blood lipid levels.

Policosanol in Elderly Patients

Policosanol administered for short or long-term in patients over the age of 60 years with hypercholesterolemia has been effective, safe and well tolerated.^{44,45} In this population policosanol has a similar efficacy profile to that observed in patients below 60 years old. Table 3 summarizes the main results obtained at months 6 and 12 in a long-term study performed in elderly patients. Of particular importance in this population is the fact that no drug-related adverse experiences have been shown. Elderly patients are at risk for such problems due to impaired renal and hepatic clearance as well as a high coexistence of concomitant diseases and of medications consumption are present.

Table 3. Effect of policosanol on the serum lipid profile in elderly patients with hypercholesterolemia				
<i>Treatment</i>	<i>Baseline</i>	<i>6 months</i>	<i>12 months</i>	<i>Percent change</i>
Total cholesterol (mmol/L)				
Policosanol	7.68	6.67	6.43	-16.4
Placebo	7.33	7.46	7.57	+0.03
LDL-C (mmol/L)				
Policosanol	5.40	4.34	4.10	-24.1
Placebo	4.99	5.22	5.24	+4.8
HDL-C (mmol/L)				
Policosanol	1.28	1.28	1.36	+5.9

Placebo	1.28	1.25	1.25	-2.4
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Patients with Type II Hypercholesterolemia and Disturbances of Hepatic Function

The efficacy pattern of policosanol in patients with type II hypercholesterolemia and concomitant disturbances of hepatic function is similar to that shown in hypercholesterolemic patients without impairment of liver function.⁴⁶ Policosanol reduced total cholesterol (-13.6%), LDL-C (-19.1%), LDL-C to HDL-C ratio (-25.5%) and raised HDL-C (+11.5%). In addition, policosanol was shown to reduce levels of alanine aminotransferase (ALT) and gamma-glutamyltranspeptidase (GGT) toward normal values.

Policosanol in the Nephrotic Syndrome

Policosanol reduced effectively total cholesterol, LDL-C and triglycerides values while increasing HDL-C levels in patients with the nephrotic syndrome without adversely affecting renal function.⁴⁷

IX. ANTI-PLATELET EFFECTS

Policosanol reduces platelet aggregation by altering prostaglandin synthesis. Specifically, policosanol lowers serum levels of the pro-aggregatory thromboxane A₂, while increasing the anti-aggregatory prostaglandin prostacyclin. Clinical trials in humans have shown that policosanol significantly inhibits platelet aggregation without affecting coagulation parameters.⁹⁻¹¹ Policosanol's effects on platelet aggregation compare quite favorably to low-dose aspirin.⁴⁸

	<i>Baseline</i>	<i>After treatment</i>	<i>Difference</i>
Arachidonic acid 0.5 mM			
Policosanol	68.5	43.3	-25.2
Placebo	70.0	72.5	+2.6
Epinephrine 1.25 x 10⁻⁵ M			
Policosanol	63.8	46.0	-17.8
Placebo	59.1	62.8	+3.8
Collagen 0.5 mcg/ml			
Policosanol	67.7	51.8	-16.0
Placebo	64.0	67.5	+3.6
ADP 2 x 10⁻⁶ M			
Policosanol	56.7	50.9	-5.8
Placebo	54.7	57.9	+3.2

X. EFFECTS IN IMPROVING ANGINA

Policosanol was shown to improve the clinical evolution, and exercise-ECG testing responses of coronary heart disease (CHD) patients with myocardial ischemia, documented by exercise myocardial perfusion scintigraphy.⁴⁹ In the double-blind study, 15 patients were treated with 5 mg of policosanol twice daily; another 15 patients were administered the same dose plus 125 mg aspirin; and the other 15 patients received placebo plus equal aspirin dose. They were followed for 20 months, previous baseline observations, with treadmill exercise-ECG, besides serum lipid test. Beneficial changes on proportions among the 2 policosanol groups and the placebo group, showed an increment on functional capacity class, a decrement on rest and exercise angina, and a significant decrease in cardiac events, and in ischemic ST segment response, especially in the policosanol plus aspirin group.

XI. SIDE EFFECTS, SAFETY AND TOXICOLOGY

Policosanol exhibits an exemplary safety profile. In all controlled studies, policosanol has exerted no negative effect of any clinical or laboratory parameter. Side effects were comparable to a placebo. In fact, the withdrawal rate for policosanol in short and long-term clinical studies was comparable or even lesser than that of placebo; only 0.2 % policosanol-patients withdrew before conclusion of the study as a result of an adverse experience, compared with 0.6 % of placebo patients. Comparative studies have shown a dropout rate due to side effects of 0.9% in policosanol-treated patients compared with a 4.4% rate for those treated with other lipid-lowering drugs (e.g., statins, fibrates, probucol, and acipimox). In a large post marketing surveillance study, the tolerability of policosanol was assessed in 27,879 patients (17,225 patients for two years and 10,654 patients for four years). All of the patients were treated for at least one month. During the study, 86 patients (0.31%) reported adverse effects, the most frequent of which was weight loss. Twenty-two (0.08%) discontinued treatment because of presumed side effects.⁵⁰ A single dose (1,000 mg/day) as much as 50 times the maximum recommended dose (20 mg/day) administered to healthy volunteers produced no adverse reaction, hence no over dosage symptoms have been detected. Animal studies demonstrate the policosanol is virtually non-toxic as the oral LD₅₀ in rats, mice, rabbits and dogs was > 5 000 mg/kg. Body weight gain, behavioral assays, as well as biochemical and hematological determinations in surviving animals at the end of the test (14 days) did not reveal differences

between treated and control groups. Moreover, weight organ analysis and histopathological study did not reveal differences between groups.^{51,52} The effects of successive dosage increases of policosanol administered orally to *Macaca arctoides* monkeys demonstrated that even the highest dose administered (500 mg/kg) Policosanol was tolerated. Similar results have been shown oral subchronic and chronic toxicity models in rats, dogs, and monkeys.⁵³⁻⁵⁵ Policosanol did not produce any adverse effects on fertility and reproduction in animal studies, nor has it exerted any mutagenic or carcinogenic effects.⁵⁶⁻⁶⁰ Specifically, policosanol administered orally up to 500 and 1000 mg/kg during the organogenesis period did not produce embryotoxic nor teratogenic effects in rats or rabbits and a multigenerational study did not show any toxicity.

XII. CONTRAINDICATIONS

Pregnancy

Although policosanol neither induced teratogenic effects in rats or rabbits nor affected rat fertility and reproduction, the treatment is not allowed to use in pregnant women. The reason for this restriction is that cholesterol and associated metabolic products are required for an adequate fetal development. Since hypercholesterolemia and atherosclerosis are chronic diseases, the suspension of lipid-lowering therapy for 9 months cannot be considered as an additional coronary risk factor.

Lactation

It is not known whether the product or some active metabolite is excreted via the human milk during nursing, therefore therapy should be discontinued during lactation.

Pediatric use

Efficacy and safety of policosanol in children has not been well established. Thus, treatment of children with policosanol is not recommended at the present.

XIII. DRUG INTERACTIONS

Policosanol has demonstrated synergism with the anti-platelet properties of aspirin in experimental animal models and healthy human volunteers as well as in different experimental animal models of ischemia and thrombosis. Pretreatment with policosanol inhibited aspirin-induced gastric ulcer in experimental animals.

Anticoagulants

Single or repeated doses of policosanol administered orally did not significantly affect fibrinolytic activity or bleeding time in rats. In these studies interaction between policosanol and heparin or warfarin have been ruled out.⁶¹

Antipyrene and theophylline

Antipyrene is a model drug used to investigate interaction with drugs metabolized by liver microsomal enzymes (the P-450 system). Policosanol administered orally to Beagle dogs for 3 to 4 weeks did not affect antipyrene or theophylline pharmacokinetics, suggesting that it does not interact with drugs metabolizing processes involving the P-450 microsomal system.

Other concomitant therapies

Although no specific clinical trials have been developed to evaluate its possible pharmacological interactions, in short and long-term clinical studies, policosanol has been simultaneously employed with calcium antagonists, inhibitors of angiotensin-converting enzyme, beta-blockers, meprobamate, diuretics, nitroderivative vasodilators, non-steroidal anti-inflammatory drugs, anxiolytics, anti-depressant, neuroleptics, oral hypoglycemic agents, digoxin, warfarin, thyroid hormones, anti-ulcer drugs, between others without evidence of clinically relevant adverse interactions.

XIV. SUMMARY

Policosanol is a mixture of fatty alcohols derived from the wax of sugar cane. These active substances work to lower cholesterol levels by several mechanisms. It inhibits cholesterol manufacturer but does so prior to HMG-CoA reductase. In addition policosanol also exerts exceptional effects on LDL-cholesterol metabolism. Specifically, policosanol increases LDL receptor processing. It exerts this effect by increasing the binding of LDL to its receptor, improving the transport of LDL into the liver cell, and significantly enhancing the breakdown of LDL cholesterol. In addition to lowering LDL, policosanol has also been shown to increase HDL, protect against free radical damage to LDL-cholesterol, and inhibit excessive platelet aggregation. All together, policosanol exerts many pharmacological actions of benefit in the prevention and treatment of atherosclerosis or hardening of the arteries. The clinical documentation for policosanol is exceptional. Well-designed clinical trials have included short and long-term, randomized, double-blind studies comparing policosanol to a placebo as well as double-blind comparative trials versus statin drugs, fibrates, acipimox, and probucol. Policosanol produces cholesterol-lowering effects within the first 6-8 weeks of use. At a daily dosage of 10 mg of policosanol at night, LDL cholesterol levels typically drop by 20 to 25% within the first six months of therapy. At a dosage of 20 mg, LDL levels typically drop by 25-30%. HDL cholesterol levels typically increase by 15 to 25% after only two months of use. The combined LDL reduction and HDL increase can produce dramatic improvements in the LDL to HDL ratio. These improvements in lipid profiles compare quite favorably to results observed with statin drugs. From comparative studies it can be concluded that 10 mg of policosanol is equivalent in efficacy to 20 mg of lovastatin and 10 mg of simvastatin and pravastatin. But, while these drugs have well-known side effects, policosanol is completely safe. Policosanol has not been shown to produce any adverse drug interaction as well and it can be used in diabetics, elderly subjects, and even in patients with impaired liver function or severe liver damage without fear of side effect. The recommended dosage of policosanol is 10 mg at the evening meal. It is given at night because most cholesterol manufacture occurs at night. As with other cholesterol-lowering therapies, dosage can be adjusted based upon checking the blood cholesterol levels every two months.

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