CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-249

ADMINISTRATIVE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expuation Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Kos Pharmaceuticals, Inc.
1001 Brickell Bay Drive, 25th Floor, Miami, FL 33131

2. TELEPHONE NUMBER *(Include Area Code)*

(305) 512-7051

3. PRODUCT NAME

Nicostatin (Niacin Extended-Release and Lovastatin Tablets)

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

4021

6. LICENSE NUMBER / NDA NUMBER

NDA 21-249

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

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Labeling

Division of Metabolic and Endocrine Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 21-249

Name of Drug: Advicor (extended release niacin and lovastatin) Tablets

Sponsor: Kos Pharmaceuticals , Inc.

Material Reviewed

Submission Date(s): September 21, 2000 (package insert and immediate container labels), and July 19, 2001 (Package insert)

Receipt Date(s): September 22, 2000; July 20, 2001

Background and Summary Description: This review compares the package insert submitted in this new NDA with the final draft labeling negotiated with the Division.

Review

Deletions are shown as ~~strikeouts~~ and additions are shown as double underlines. The following revisions were noted:

Package insert

The submitted package insert, identified as "Industry Version of September 21, 2000", was compared to the package insert, identified as "Kos Final Version 16-July-2001".

1. In the **DESCRIPTION** section:

PROPOSED

APPROVED

ADVICOR contains niacin extended-release and lovastatin in combination.

2. In the **CLINICAL PHARMACOLOGY** section:

PROPOSED

APPROVED

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B-100 (Apo B) promote human atherosclerosis. Similarly, decreased levels of high-density lipoprotein cholesterol (HDL-C) are associated with the development of atherosclerosis. Epidemiological investigations have established that cardiovascular morbidity and mortality vary directly with the level of TC and LDL-C, and inversely with the level of HDL-C.

Cholesterol-enriched triglyceride-rich lipoproteins, including very low-density lipoproteins (VLDL), intermediate density lipoproteins (IDL), and their remnants, can also promote atherosclerosis. Elevated plasma triglycerides (TG) are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease (CHD). As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD.

3. In the **Effects on Lipids** subsection:

PROPOSED

[ ]

APPROVED

ADVICOR reduces LDL-C, TC, and TG, and increases HDL-C due to the individual actions of niacin and lovastatin.

4. In the **Mechanism of Action** subsection:

PROPOSED

[ ]

APPROVED

The mechanism by which niacin alters lipid profiles is not completely understood and 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-C and LDL-C, and does not appear to affect fecal excretion of fats, sterols, or bile acids.

5. In the **Pharmacokinetics** subsection, Absorption and Bioavailability paragraphs

PROPOSED

[

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APPROVED

The extent of niacin absorption from Advicor was increased by administration with food. The administration of two ADVICOR 1000/20 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 Cmax 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 condition.

6. In the **Pharmacokinetics** subsection, Elimination paragraphs:

PROPOSED

APPROVED

Niacin is primarily excreted in urine mainly as metabolites.

7. In the **Special Populations** subsection, Gender paragraph:

PROPOSED

[

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APPROVED

The gender differences observed in plasma niacin and metabolite levels may be due to gender-specific differences in metabolic rate or volume of distribution. Data from clinical trials suggest that women have a greater hypolipidemic response than men at equivalent doses of NIASPAN and ADVICOR.

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In a multi-center, randomized, double-blind, parallel, 28-week, active-comparator study in patients with Type IIa and IIb hyperlipidemia, 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. Up to a third of the patients randomized to ADVICOR or NIASPAN

discontinued prior to Week 28. In this study, ADVICOR decreased LDL-C, TG and Lp(a), and increased HDL-C in a dose-dependent fashion (Tables 2, 3, 4 and 5 below). Results from this study for LDL-C mean percent change from baseline (the primary efficacy variable) showed that:

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 2000/40 ($p<.0001$)
2) ADVICOR at doses of 1000/20 or higher achieved greater LDL-lowering than NIASPAN ($p<.0001$)

The LDL-C results are summarized in Table 2:

Table 2. LDL-C mean percent change from baseline

Week	ADVICOR			NIASPAN			Lovastatin		
	n*	Dose	LDL	n*	Dose	LDL	n*	Dose	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 HDL-raising compared to lovastatin and NIASPAN monotherapy at all doses (Table 3).

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Table 3. HDL-C mean percent change from baseline

Week	ADVICOR			NIASPAN			Lovastatin		
	n*	Dose	HDL	n*	Dose	HDL	n*	Dose	HDL
Baseline	57	-	45 mg/dl	61	-	47 mg/dl	61	-	43mg/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 or greater compared to lovastatin and NIASPAN monotherapy (Table 4).

Table 4. TG median percent change from baseline

Week	ADVICOR			NIASPAN			Lovastatin		
	n*	Dose	TG	n*	Dose	TG	n*	Dose	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 5). 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 5. Lp(a) median percent change from baseline

Week	ADVICOR			NIASPAN			Lovastatin		
	n	Dose	Lp(a)	n	Dose	Lp(a)	n	Dose	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 Long-Term Study

A total of 814 patients were enrolled in a long-term (52-week), open-label, single-arm study of ADVICOR. Patients were force dose-titrated to 2000/40 over 16 weeks. After titration, patients were maintained on the maximum tolerated dose of ADVICOR for a total of 52 weeks. Five hundred-fifty (550) patients (68%) completed the study, and fifty-six percent (56%) of all patients were able to maintain a dose of 2000/40 for the 52 weeks of treatment. The lipid-altering effects of ADVICOR peaked after 4 weeks on the maximum tolerated dose, and were maintained for the duration of treatment. These effects were comparable to what was observed in the double-blind study of ADVICOR (Tables 2—).

9. In the **INDICATIONS AND USAGE** section:

PROPOSED

APPROVED

ADVICOR is a fixed dose combination product and is not indicated for initial therapy (see Dosage and Administration). 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. Initial medical therapy is indicated with a single agent 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 (see also Table 7 and the NCEP treatment guidelines[1]).

ADVICOR is indicated for the treatment of primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson Types IIa and IIb; Table 6) in:

- Patients treated with lovastatin who require further TG lowering or HDL raising who may benefit from having niacin added to their regimen
- Patients treated with niacin who require further LDL lowering who may benefit from having lovastatin added to their regimen

10. In the **General Recommendations** subsection:

PROPOSED

APPROVED

Prior to initiating therapy with a lipid-lowering agent, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure TC, HDL-C, and TG. For patients with TG < 400 mg/dL, LDL-C can be estimated using the following equation:

LDL-C = TC – [(0.20 x TG) + HDL-C]

For TG levels > 400 mg/dL, this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. Lipid determinations should be performed at intervals of no less than 4 weeks and dosage adjusted according to the patient's response to therapy. The NCEP Treatment Guidelines are summarized in Table 7.

Table 7. NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD[†] or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)[††]
2+ Risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk factor[†††]	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

[†] CHD, coronary heart disease

[††] Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.

[†††] Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

11. In the **CONTRAINDICATIONS** section:

PROPOSED

APPROVED

ADVICOR is contraindicated in patients with a known hypersensitivity to niacin, lovastatin or any component of this medication, active liver disease or unexplained persistent elevations in serum transaminases (see Warnings), active peptic ulcer disease, or arterial bleeding.

Pregnancy and lactation – Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase, such as lovastatin, to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, ADVICOR is contraindicated in women who are pregnant and in lactating mothers. ADVICOR may cause fetal harm when administered to pregnant women. **ADVICOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive.** If the patient becomes pregnant while taking this drug, ADVICOR should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus (see PRECAUTIONS, Pregnancy).

12. In the **WARNINGS** section, **Liver Dysfunction** subsection:

PROPOSED

APPROVED

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 elevations[2]. In three safety and efficacy studies involving titration to final daily ADVICOR doses ranging from 500/10 to 2500/40, ten of 1028 patients (1.0%) experienced reversible elevations in AST/ALT to more than 3 times the upper limit of normal (ULN). Three of ten elevations occurred at doses outside the recommended dosing limit of 2000/40; no patient receiving 1000/20 had 3-fold elevations in AST/ALT.

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

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Lovastatin

Lovastatin and other inhibitors of HMG-CoA reductase occasionally cause myopathy, which is manifested as muscle pain or weakness associated with grossly elevated creatine kinase (> 10 times ULN). **Rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, has been reported rarely and can occur at any time.** In a large, long-term, clinical safety and efficacy study (the EXCEL study)[3,4] with lovastatin, myopathy occurred in up to 0.2% of patients treated with lovastatin 20 to 80 mg for up to 2 years. When drug treatment was interrupted or discontinued in these patients, muscle symptoms and creatine kinase (CK) increases promptly resolved. The risk of myopathy is increased by concomitant therapy with certain drugs, some of which were excluded by the EXCEL study design.

The risk of myopathy appears to be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Lovastatin is metabolized by the cytochrome P450 isoform 3A4. Certain drugs which share this metabolic pathway can raise the plasma levels of lovastatin and may increase the risk of myopathy. These include cyclosporine, itraconazole, ketoconazole and other antifungal azoles, the macrolide antibiotics erythromycin and clarithromycin, HIV protease inhibitors, the antidepressant nefazodone, or large quantities of grapefruit juice (>1 quart daily).

ADVICOR

Myopathy and/or rhabdomyolysis have been reported when lovastatin is used in combination with lipid-altering doses (>1g/day) of niacin. Physicians contemplating the use of ADVICOR, a combination of lovastatin and 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, no cases of rhabdomyolysis and one suspected case of myopathy have been reported in 1079 patients who were treated with ADVICOR at doses up to 2000/40 for periods up to 2 years.

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.

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 (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.

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14. In the **PRECAUTIONS** section, **General** subsection:

PROPOSED

APPROVED

Diabetic patients may experience a dose-related rise in fasting blood sugar (FBS). In three clinical studies, which included 1028 patients exposed to ADVICOR (6 to 22% of whom had diabetes type II at baseline), increases in FBS above normal occurred in 46 to 65% of patients at any time during study treatment with ADVICOR. Fourteen patients (1.4%) were discontinued from study treatment: 3 patients for worsening diabetes, 10 patients for hyperglycemia and 1 patient for a new diagnosis of diabetes. In the studies in which lovastatin and NIASPAN were used as active controls, 24 to 41% of patients receiving lovastatin and 43 to 58% of patients receiving NIASPAN also had increases in FBS above normal. One patient (1.1%) receiving lovastatin was discontinued for hyperglycemia. Diabetic or potentially diabetic patients should be observed closely during treatment with ADVICOR, and adjustment of diet and/or hypoglycemic therapy may be necessary.

In one long-term study of 106 patients treated with ADVICOR, elevations in 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 count (mean of –11% with 2000 mg) and increases of PT (mean of approximately +4%). Accordingly, patients undergoing surgery should be carefully evaluated. In controlled studies, ADVICOR has been associated with small but statistically significant dose-related reductions in phosphorus levels (mean of -10% with 2000/40). Phosphorus levels should be monitored periodically in patients at risk for hypophosphatemia. In clinical studies with ADVICOR, hypophosphatemia was more common in males than in females. The clinical relevance of hypophosphatemia in this population is not known.

15. In the **Pregnancy** subsection:

PROPOSED

APPROVED

Niacin

Animal reproduction studies have not been conducted with niacin or with ADVICOR. It is also not known whether niacin at doses typically 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 for primary hypercholesterolemia (Types IIa or IIb) becomes pregnant, the drug should be discontinued.

16. In the **Geriatric Use** subsection:

PROPOSED

APPROVED

Of the 214 patients who received ADVICOR in double-blind clinical studies, 37.4% were 65 years-of-age and older, and of the 814 patients who received ADVICOR in open-label clinical studies, 36.2% were 65 years-of-age and older. Responses in LDL-C, HDL-C, and TG were similar in geriatric patients. No overall differences in the percentage of patients with adverse events were observed between older and younger patients. No overall differences were observed in selected chemistry values between the two groups except for amylase which was higher in older patients.

17. In the **ADVERSE REACTIONS** section, **Overview** subsection:

PROPOSED

APPROVED

In controlled clinical studies, 40/214 (19%) of patients randomized to ADVICOR discontinued therapy prior to study completion, 18/214 (8%) of discontinuations being due to flushing. In the same controlled studies, 9/94 (10%) of patients randomized to lovastatin and 19/92 (21%) of patients randomized to NIASPAN also discontinued treatment prior to study completion secondary to adverse events. Flushing episodes (i.e., warmth, redness, itching and/or tingling) were the most common treatment-emergent adverse events, and occurred in 53% to 83% of patients treated with ADVICOR. Spontaneous reports with NIASPAN and clinical studies with ADVICOR suggest that flushing may also be accompanied by symptoms of dizziness or syncope, tachycardia, palpitations, shortness of breath, sweating, chills, and/or edema.

18. In the **Adverse Reactions Information** subsection:

PROPOSED

APPROVED

The data described in this section reflect the exposure to ADVICOR in two double-blind, controlled clinical studies of 400 patients. The population was 28 to 86 years-of-age, 54% male, 85% Caucasian, 9% Black, and 7% Other, and had mixed dyslipidemia (Frederickson Types IIa and IIb).

In addition to flushing, other adverse events occurring in 5% or greater of patients treated with ADVICOR are shown in Table 8 below.

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Table 8 Treatment-Emergent Adverse Events in ≥ 5% of Patients Events Irrespective of Causality, Controlled, Double-Blind Studies

Adverse Event	ADVICOR	NIASPAN	Lovastatin
Total Number of Patients	214	92	94
Cardiovascular	**163 (76%)**	**66 (72%)**	**24 (26%)**
Flushing	152 (71%)	60 (65%)	17 (18%)
Body as a Whole	**104 (49%)**	**50 (54%)**	**42 (45%)**
Asthenia	10 (5%)	6 (7%)	5 (5%)
Flu Syndrome	12 (6%)	7 (8%)	4 (4%)
Headache	20 (9%)	12 (13%)	5 (5%)
Infection	43 (20%)	14 (15%)	19 (20%)
Pain	18 (8%)	3 (3%)	9 (10%)
Pain, Abdominal	9 (4%)	1 (1%)	6 (6%)
Pain, Back	10 (5%)	5 (5%)	5 (5%)
Digestive System	**51 (24%)**	**26 (28%)**	**16 (17%)**
Diarrhea	13 (6%)	8 (9%)	2 (2%)
Dyspepsia	6 (3%)	5 (5%)	4 (4%)
Nausea	14 (7%)	11 (12%)	2 (2%)
Vomiting	7 (3%)	5 (5%)	0
Metabolic and Nutrit. System	**37 (17%)**	**18 (20%)**	**13 (14%)**
Hyperglycemia	8 (4%)	6 (7%)	6 (6%)
Musculoskeletal System	**19 (9%)**	**9 (10%)**	**17 (18%)**
Myalgia	6 (3%)	5 (5%)	8 (9%)
Skin and Appendages	**3 (2%)**	**19 (21%)**	**11 (12%)**
Pruritus	14 (7%)	7 (8%)	3 (3%)
Rash	11 (5%)	11 (12%)	3 (3%)

Note: Percentages are calculated from the total number of patients in each column.

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19. In the **DOSAGE AND ADMINISTRATION** section:

PROPOSED

APPROVED

ADVICOR should be taken at bedtime, with a low-fat snack, and the dose should be individualized according to patient response.

The usual recommended starting dose for NIASPAN is 500 mg qhs. NIASPAN must be titrated and the dose should not be increased by more than 500 mg every 4 weeks up to a maximum dose of 2000 mg a day, to reduce the incidence and severity of side effects. Patients already receiving a stable dose of NIASPAN may be switched directly to a niacin-equivalent dose of ADVICOR.

The usual recommended starting dose of lovastatin is 20 mg once a day. Dose adjustments should be made at intervals of 4 weeks or more. Patients already receiving a stable dose of lovastatin may receive concomitant dosage titration with NIASPAN, and switch to ADVICOR once a stable dose of NIASPAN has been reached.

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

20. All references to the drug name NICOSTATIN in the "PROPOSED" paragraphs, have been changed to ADVICOR in the "APPROVED" paragraphs.

Bottle/Vial Label

It is recommended that the applicant submit mock-ups of immediate container labels for all container sizes with the following revisions:

- insert an image of the company logo in place of the word "LOGO."
- describe strength using "mg" after both numbers; i.e., 500mg/20mg, 750mg/20mg, and 1000mg/20mg.
- express storage temperature as "°C" and "°F" instead of ' — ' and " — " as was originally submitted in the *.pdf* file.
- provide mock-ups of immediate container labels for the 90 count in a 200 cc bottle presentation for all three strengths.

Conclusions

The package insert submitted on July 19, 2001, is acceptable.

The current labeling is now considered: Approvable

Package insert: Approvable
Bottle/Vial label: minor editorial changes needed
Carton: none submitted

{See appended electronic signature page}

William C. Koch, R.Ph. Date
Regulatory Project Manager

{See appended electronic signature page}

Enid Galliers Date
Chief, Project Management Staff

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William Koch
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Enid Galliers
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CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 12/20/00	**DUE DATE:** 04/01/01	**OPDRA CONSULT #:** 01-0015

TO:

David Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH:

William C. Koch
Project Manager
HFD-510

PRODUCT NAME: —— (Primary) and Advicor (Alternate) (niacin extended-release and lovastatin tablets) 500 mg/20 mg, 750 mg/20 mg and 1000 mg/20 mg **NDA:** 21-249	**MANUFACTURER BY:** Kos Pharmaceuticals, Inc.

SAFETY EVALUATOR: David Diwa Pharm.D.

SUMMARY: In response to a consult from the Division of Metabolic and Endocrine Drug Products (HFD-510), OPDRA has performed a review of the proposed proprietary names —— (primary) and Advicor (alternate) to determine the potential for confusion with marketed drug products and pending drug names.

OPDRA RECOMMENDATION: OPDRA has no objection to the use of the proposed name —— or Advicor. However, we concur with DDMAC that the name —— is objectionable from an advertising and promotional perspective.

☒ FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

☐ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

☐ FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

Martin Himmel, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 03/12/01

NDA: 21-249

NAME OF DRUG: ——— (Primary) and Advicor (Alternate)
(niacin extended-release and lovatatin tablets)
500 mg/20 mg, 750 mg/20 mg and 1000 mg/20 mg

NDA HOLDER: Kos Pharmaceuticals, Inc

I. INTRODUCTION:

This consult is written in response to a December 20, 2000 request from the Division of Metabolic & Endocrine Drug Products (HFD-510) for an assessment of the proposed proprietary name, ——— and alternate name Advicor.

PRODUCT INFORMATION

——— /Advicor is a combination of niacin (extended-release) and lovastatin. Niacin (nicotinic acid) is a water-soluble B-complex vitamin and component of two coenzymes used in the adjunctive treatment of hyperlipidemias. Lovastatin is an HMG-CoA reductase inhibitor that is indicated for the treatment of elevated cholesterol. ——— /Advicor is indicated as an adjunct to diet for the reduction of elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), ——— and plasma triglycerides (TG). The product is also indicated for [redacted] In addition, patients who have failed on diet alone may be given ——— /Advicor to increase high-density lipoprotein cholesterol (HDL-C). ——— /Advicor should not be given to patients with significant or unexplained hepatic dysfunction, active peptic ulcer disease or arterial bleeding. The drug is also contraindicated in women who are pregnant or nursing.

The proposed initial dose is one 500 mg/20 mg tablet taken at bedtime following a low-fat snack daily for at least 4 weeks. The dose may be increased to 1000 mg/40 mg
(2 tablets) based on response. Some patients may be controlled with one 1000 mg/20 mg dose, however, the niacin dose should not be increased by more than 500 mg per day in any 4-week period. Women may respond to lower doses than men. The sponsor does not recommend doses greater than 2000 mg/40 mg per day. ———/Advicor will be available in 500 mg/20 mg, 750 mg/20 mg and 1000 mg/20 mg tablets packaged in bottles of 30 and180. The product can be stored at room temperature (20 to 25°C or 68 to 77°F).

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound alike or look alike to [redacted] /Advicor to a degree where potential confusion between drug names could occur under usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the proposed names [redacted] /Advicor.

A. EXPERT PANEL DISCUSSION

The expert panel consists of members of OPDRA's medication error Safety Evaluator Staff and a representative from the Division of Drug Marketing, Advertising and Communications (DDMAC).

Several names identified by the Expert Panel were thought to have the potential for confusion with [redacted] Advicor. These products are summarized in the table below. In addition, the panel felt that there was a question of claim in the name [redacted].

DDMAC has no objection to the proposed name Advicor. However, the Division objects to the proposed name [redacted] because it is too close to [redacted], thus an overstatement of the product's effectiveness. DDMAC contends that although lipid-lowering agents reduce the risk of cardiovascular morbidity and mortality, they do not offer complete protection from such risk and is therefore misleading.

Product Name	Dosage form(s), Generic name	Usual Dose	Observation
[redacted] Advicor	Tablet; (niacin extended release/lovastatin)	500 mg/ 20 mg tablet: 1 to 2 daily	
Primacor	Injectable; (milrinone)	0.5 mcg/kg/min	LA/SA*
Pilocar	Tablet, Gel, Solution; (pilocarpine)	5 mg 3 times daily 0.5" gel ribbon once daily 1-2 drops 2-4 times daily	LA/SA*
Proscar	Tablet; (finasteride)	5 mg daily	LA/SA*
[redacted]			LA/SA*
Advil (OTC)	Tablet/caplets (ibuprofen)	200 mg tab every 4 to 6 hours	LA/SA*
Mevacor	Tablet (lovastatin)	20 mg daily	SA*
Acova	Injectable (argatroban)	2 mcg/kg/min	LA/SA*

*SA = Sound-alike
*LA = Look-alike

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).
[2] American Drug Index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.
[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[4] The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.
[5] WWW location http://www.uspto.gov/tmdb/index.html.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three studies were conducted by OPDRA involving 86 health professionals comprised of pharmacists, physicians, and nurses within the FDA. The objective was to test the degree of name confusion between ——— /Advicor and other drug names due to similarity in handwriting and verbal pronunciation of the name. Inpatient and outpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for ——— /Advicor (see below). These prescriptions were scanned into a computer and subsequently delivered to a random sample of the participating health professionals via e-mail. In addition, the verbal order was recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient Rx: ——— 500 mg/20 mg i qhs	Verbal Rx: ——— 500/20 mg qhs
Inpatient Rx: ——— 500 /20 mg qhs	

ADVICOR

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient Rx: advicor 500/20 mg i tab Qhs	Verbal Rx: advicor 500/20 mg i tab mg qhs
Inpatient Rx: advicor 500 /20 mg qhs	

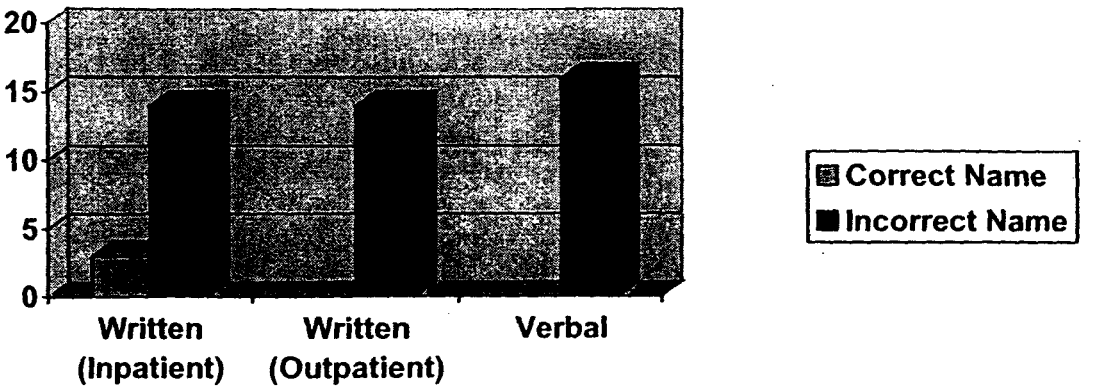
2. The results are summarized in Table I below.

Table Ia

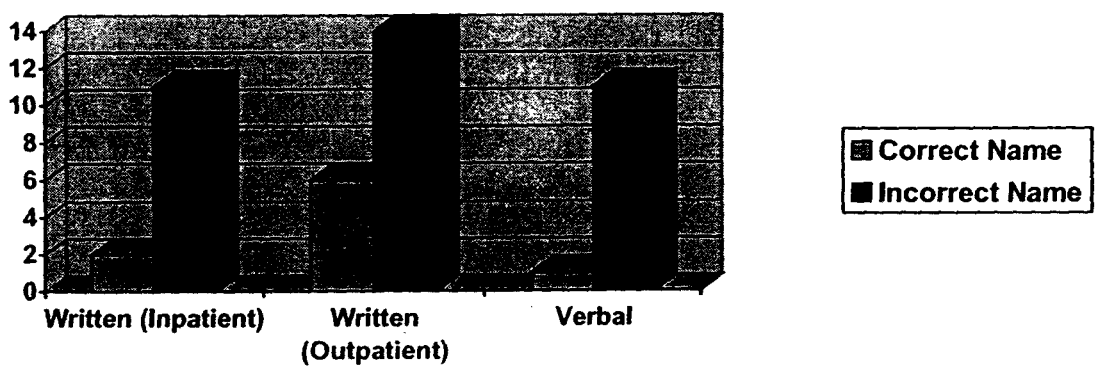
Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	28	17 (63%)	3 (18%)	14 (82%)
Written Outpatient	30	14 (47%)	0 (0%)	14 (100%)
Verbal	28	16 (57%)	0 (0%)	16 (100%)
Total	86	47 (55%)	3 (6%)	44 (94%)

Table Ib (ADVICOR)

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	30	13 (43%)	2 (15%)	11 (85%)
Written Outpatient	28	20 (71%)	6 (30%)	14 (70%)
Verbal	28	11 (39%)	1 (9%)	10 (91%)
Total	86	46 (53%)	10 (22%)	36 (78%)



ADVICOR



Ninety four percent of all ——— study participants and seventy four percent of all Advicor participants responded incorrectly to the proposed names. Written and verbal scores of the incorrect responses are summarized in Table II on page 6.

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Table IIa

Incorrectly Interpreted	
Written Outpatient	
Verbal	
Written Inpatient	

Table IIb

Incorrectly Interpreted	
Written Outpatient	Adericon (2)
	Adericor
	Adreicor
	Adrican
	Aduicar
	Aduiceer
	Adulcar
	Adulcer
	Advicar
	Advicare
	Adviceer (2)
	Dau???
Verbal	Adracor
	Advacor (2)
	Advacore
	Advachor
	Advecor
	Advocor
	Avacor (2)
	Avicor
Written Inpatient	Adevior
	Adivicor
	Adivor
	Adurior
	Adurisor
	Adurizor
	Aduzior
	Advisor (3)
	Adwior

All incorrect responses in the ——— and Advicor prescription studies were misspelled or phonetic variations of the proposed drug names. Overall, there were more incorrect responses in the —— studies (94%) than in the Advicor studies (78%). None of the inaccurate responses overlapped with an existing approved drug product.

The ——— studies showed definite patterns of incorrect responses suggesting that penmanship and verbal pronunciation of the proposed name were strong determinants of the response. In the written outpatient study 10 out of 14 participants (71%) incorrectly responded with ——— In the written inpatient study, 11 out of 17 participants (65%) incorrectly responded with ——— The verbal study showed a similar result with 11 out of 16 participants (69%) incorrectly responding with ——— The proposed name was misspelled on the outpatient written prescription order as ——— rather than ——— thus affecting the result of the study.

In the Advicor stuidies, the last for letters "vicor" were misinterpreted in almost all the incorrest responses. There was no definite pattern of incorrect responses as compared to the ——— studies. The verbal study showed the largest number of incorrect responses (10 out of 11). There was a difference in the number of incorrect responses between the written outpatient (70%) and written inpatient (91%) result also suggesting the influence of penmanship.

C. SAFETY EVALUATOR RISK ASSESSMENT

(i) In reviewing the proposed name ——— the expert panel identified ——— Primacor, Pilocar and Proscar as most problematic with the potential for name confusion. All the names identified look and sound like ———

Primacor is an injectable dosage form of milrinone, a phosphodiesterase inhibitor with positive inotropic and vasodilator activity. It is indicated for the short-term management of severe congestive heart failure unresponsive to other forms of therapy and in the treatment of acute heart failure following cardiac surgery. The name Primacor looks and sounds similar to ——— However, Primacor is available, as an injectable dosage form while ——— will be available in tablet form. The two drugs have different routes of administration, dosing interval and will not likely be stored in close proximity due to the difference in formulation. Additionally, Primacor is used primarily by cardiologists and dosed by body weight. The risk of a product mix-up due to name confusion between Primacor and ——— appears to be minimal.

Pilocar (pilocarpine) is a cholinergic agent used primarily to treat glaucoma. Pilocar is available as a gel, solution and tablet. The oral formulation is used for symptomatic treatment of xerostomia. Pilocar and ——— belong to different pharmacologic classes and are used for different indications. The oral formulation of Pilocar is available in 5 mg tablets while ——— will be available in tablets of 500 mg/20 mg, 750 mg/20 mg and 100 mg/20 mg. The potential risk of confusing Pilocar with ——— is low.

Proscar is a tablet formulation of finasteride, which is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH), and male pattern baldness. It is available in 1 mg and 5 mg tablets as compared to ——— tablets of 500 mg/20 mg, 750 mg/20 mg and 100 mg/20 mg. Although the two drugs are dosed once daily, Proscar is generally prescribed to men and is available in much lower strengths than ———. The potential risk of name confusion between Proscar and ——— appears to be minimal.

A review of our results showed that a significant number of study participants incorrectly interpreted the proposed name as ——— instead of ——— The prescription order in the outpatient written study was incorrectly written for ——— In the verbal study, 11 out of 16 respondents (69%) incorrectly interpreted the proposed name as ——— This is significant given our sample size. We agree with DDMAC that the proposed name suggests an implied claim or offer of protection from cardiovascular disease. Since lipid-lowering agents do not offer full protection from cardiovascular disease, we are concerned that patients may view this "new" product as offering protection from dyslipidemia related cardiovascular mortality and morbidity.

(ii) In reviewing the proposed name Advicor, the expert panel identified Acova, Advil and Mevacor, as problematic with the potential for name confusion. Advil and Acova look and sound like Advicor, and Mevacor sounds like Advicor.

Acova is an injectable formulation of argatroban, a synthetic direct thrombin inhibitor. The recommended initial dose of Acova is 2 mcg/kg/min of continuous infusion. Acova and Advicor will be provided in different dosage forms. Advicor will be available in tablet dosage form with a usual dose of 500 mg/20 mg 1 to 2 times daily. Acova is mostly used in hospital settings, while Advicor will be used in all patient care settings. Moreover, the major use of Advicor will be in outpatient care settings. Acova and Advicor will not likely be stored in close proximity, thus minimizing the risk of product mix-up. Acova is an injectable solution which is stable between 15°C to 30 °C (59 - 86 °F) for 24 hours after reconstitution. It can also be stored between 2 to 8 °C for up to 48 hours. Although the prorietary names Acova and Advicor look and sound similar, the potential for product mix-up due to name confusion is minimal.

Advil is an over the counter tablet formulation of ibuprofen. It is available in 200 mg non-prescription strength and is not likely to be confused with Advicor which will be only available by prescription.

Mevacor is a tablet formulation of lovastatin, a competitive inhibitor of HMG CoA reductase. It is a component of Advicor which, is marketed in strengths of 10 mg, 20 mg, and 40 mg. The usual dose of Mevacor is 20 mg daily at bedtime. The usual dose of Advicor is a 500 mg/20 mg tablet 1-2 times a day. Although the two products look alike and have some similarity in strength, the potential harm of inadvertently taking Mevacor instead of Advicor appears to be low.

D. STUDY SUBMITTED BY APPLICANT – **Confidential and proprietary and should be noted for FOI purposes**

[ ]

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III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the container labels and insert labeling of ——— OPDRA has attempted to focus on safety issues relating to possible medication errors. OPDRA has reviewed the current container labels, insert labeling and identified several areas of possible improvement, which might minimize potential user error.

1. CONTAINER LABEL (30s, 180s and professional sample)

   a. Revise the expression of strength to include "mg" as follows:
   500 mg/20 mg, 750 mg/20 mg, and 1000 mg/20 mg.

   b. We believe that your label devotes too much space to the company logo. The drug name and strength should have the greatest prominence and information like company names or logos should be given lesser prominence. Please revise your label to decrease the amount of space devoted to the corporate name and logo.

   c. Revise the expression of storage temperature to read as "°C" and "°F" instead of ' — ' and '— '.

   d. The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing. Your proposed container of 30 appears to be in this category. Although the container label states that the medication should be dispensed in a tight, light resistant container with a child-resistant closure, it is not clear if the manufacturer provides this container with a child-resistant closure (CRC). If CRC is not present, please revise accordingly.

   e. We note the professional blister sample pack states that before starting ———the patient should call your education program. This information does not appear on the container label or in the package insert labeling. Please clarify.

2 PACKAGE INSERT LABELING

   a. Revise the proprietary name accordingly, throughout the text of package insert.

   b. Remove the terminal zeros in tables 2 and 4 of the package insert labeling (eg. Replace 11.0 with 11).

   c. See comment 1a.

IV. RECOMMENDATIONS:

1. From a medication error perspective, OPDRA has no concern with look-alike or sound-alike similarities between ——— and other products. However, we concur with DMAC that the name ——— is objectionable from an advertising and promotional perspective.

2. OPDRA has no objection to the use of the proposed proprietary drug name Advicor.

3. OPDRA recommends implementation of the labeling changes outlined in the review to improve the safe use of this product.

We would appreciate feedback of the final outcome of this consult. We would also be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact David Diwa at 301-827-0892.

David Diwa, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

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/s/

David Diwa
4/4/01 02:54:24 PM
PHARMACIST

Jerry Phillips
4/4/01 02:55:48 PM
DIRECTOR

Martin Himmel
4/5/01 07:13:24 AM
MEDICAL OFFICER

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Patent Information Submission Form

Time Sensitive Patent Information pursuant to 21 C.F.R. 314.53 for **NDA # 20-381**

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name: **Niaspan®**

Active Ingredient(s): **niacin (nicotinic acid)**

Strength(s): **500, 750, and 1000 mg**

Dosage Form: **Extended-Release Tablets** (Solid Oral Dosage Form)

Approval Date: **July 28, 1997**

A. This information should be provided for each individual patent submitted.

U.S. Patent Number: ***6,129,930***

Expiration Date: ***September 20, 2013***

Type of Patent--Indicate all that apply:

Drug Substance (Active Ingredient) ___Y √ N

Drug Product (Composition/Formulation) √ Y __ N

Method of Use √ Y __N

a. If patent claims method(s) of use, please specify approved method(s)of use or method(s) of use for which approval is being sought that are covered by patent:

A method of treating hyperlipidemia with nicotinic acid without causing treatment-limiting elevations in uric acid or glucose levels or causing liver damage, by dosing once per day in the evening or at night

Name of Patent Owner: **Kos Pharmaceuticals, Inc.**

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US): **Not applicable**

B. The following declaration statement is required by 21 CFR § 314.53. If any of the submitted patents have Composition/Formulation or Method of Use claims, it should be submitted for each patent that contains composition/formulation or method of use claims.

The undersigned declares that the above stated United States Patent Number ***6,129,930*** covers the composition, formulation and/or method of use of Niaspan®, niacin extended-release tablets (name of drug product). This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act)

Signed: Marvin F. Blanford

Marvin F. Blanford, PharmD

Date:

Title: Vice President, Compliance

Telephone Number: 305-512-7007 or 800-211-2534, ext. 7007

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Item 14 PATENT CERTIFICATION

As required by 21 CFR §314.50 (i)(1)(i) and (ii), the following patent certifications are hereby provided for our *New Drug Application 21-249 for Nicostatin™ Tablets.*

Lovastatin component - *Paragraph III Certification*

The undersigned declares that Patent 4,231,938, belonging to Merck & Co., Inc., claims the composition of lovastatin, a component of "NICOSTATIN." "NICOSTATIN" is the subject of this application for which approval is being sought. The lovastatin patent will expire on June 15, 2001. After approval of this application, but not before June 15, 2001, Kos Pharmaceuticals intends on selling the "NICOSTATIN" product.

Niacin component - *No Relevant Patent Certification*

The undersigned also declares that to the best knowledge of Kos Pharmaceuticals, Inc., there are no relevant patents, other than the Kos Pharmaceuticals, Inc. method of use patent described in Item 13, that claim niacin component of "NICOSTATIN on which investigations that are relied upon in this application were conducted or that claim a use of niacin.

The combination of niacin and lovastatin - *No Relevant Patent Certification*

The undersigned also declares that to the best knowledge of Kos Pharmaceuticals, Inc., there are no relevant patents that claim the combination of niacin and lovastatin on which investigations that are relied upon in this application were conducted or that claim a use of combination drug.

Signed: Marvin F. Blanford

Marvin F. Blanford, PharmD

Title: Vice President of Compliance

Date: 8-17-00

Telephone Number: 305-512-7007 or 800-211-2534, ext. 7007

Item 20 OTHER – Claim for Exclusivity

(1) A statement that the applicant is claiming exclusivity.

Kos Pharmaceuticals, Inc. is claiming a 3-year period of exclusivity since new clinical investigations were conducted by the sponsor (Kos) which are essential to the approval of this application.

(2) A reference to the appropriate paragraph under§314.108.

The appropriate paragraph is §314.108(b)(4).

(3) Exclusivity claim under §314.108(2)

(Not applicable)

(4) *Information to show that the application contains "new clinical investigations" that are"essential to approval of the application" and were "conducted or sponsored by the applicant."*

(i) *New clinical investigations.*

Kos Pharmaceuticals, Inc. certifies that to the best of its knowledge, each of the clinical investigations included in this application meets the definition of a "new clinical investigation" as set forth in §314.108(a).

(ii) *Essential to approval.*

Kos Pharmaceuticals, Inc. has thoroughly searched the scientific literature. A list of all published studies or publicly available reports of clinical investigations known to the applicant through a literature search that are relevant is attached. Kos certifies that, to the best of our knowledge, the attached list is complete and accurate.

In our opinion, such published reports or publicly available reports do not provide a sufficient basis for the approval of the conditions for which Kos is seeking approval, without reference to the new clinical investigations in the application. These studies and reports are considered insufficient because:

(a) Other than studies of Nicostatin, none of the studies reported in the literature concerning the safety and efficacy of the combination of lovastatin and niacin products address a single tablet combination drug product.

(b) Other than studies of Nicostatin (and/or Niaspan®), none of the studies reported in the literature concerning the safety and efficacy of the combination of lovastatin and niacin are on once-nightly extended-release formulations of niacin.

(iii) *Conducted or sponsored by*

The new clinical studies essential for approval of this application were conducted by Kos Pharmaceuticals, Inc. under IND —— Kos Pharmaceuticals, Inc. was the sponsor named in the Form FDA-1571 for IND ——

Signed: Marvin F Blanford
Marvin F. Blanford, PharmD

Title: Vice President of Compliance

Date: 9-20-00

Telephone Number: 305-512-7007 or 800-211-2534, ext. 7007

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