CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-249

PHARMACOLOGY REVIEW(S)

NDA 21-249

Review completed: May 22, 2001

Sponsor: KOS Pharmaceutical Inc., Miami, FL.

Date Submitted: September 22, 2000.

Date Received: September 25, 2000.

Drug Class: vitamin and Statin

Category: Lipid altering, hypolipidemic

Indication: To lower lipids.

Indra Antonipillai, Ph.D.

cc: NDA Arch
HFD-510
HFD-510/davisbruno/antonipillai/parks/koch
File Name: nda21249, nicostatin, Review # 2
Safety code: AP

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REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

KEY WORDS: Statins, niacin, lipid, cholesterol, heart, dyslipidemia
Reviewer Name: Indra Antonipillai
Division Name: Division of Metabolic and Endocrine Drug products.
HFD# 510
Review Completion Date: May 22, 2001

IND/NDA number: NDA 21-249.
Serial number/date/type of submission: September 22, 2000, original submission #000.
Information to Sponsor: Yes ( ) No (X) - (labeling)
Sponsor or agent: KOS Pharmaceuticals, Inc., Miami Lakes, FL.
Manufacturer (if different) for drug substance: KOS Pharmaceuticals, Inc., Miami Lakes, FL.

Drug:
Name: Nicostatin, combination of Lovastatin and Niacin extended release

Generic Name: Nicostatin
Trade Name: Mevacor, and Niaspan
CAS Registry Number (if provided by sponsor): N/A
Chemical Name:

Product consists of a niacin (nicotinic acid) [redacted] (Niaspan®) [redacted] Lovastatin. Niaspan [redacted] will be used in strengths of 500, 750, and 1000 mg each with 20 mg of Lovastatin.

Molecular Formula/ Molecular Weight:
Nicotinic acid: $C_6H_5NO_2$; MW 123.11, pyridine-3-carboxylic acid, niacin
Lovastatin: $C_{24}H_{36}0_5$; MW 404.55; mevinolin, monacolinK, 6□ methyl compactin.

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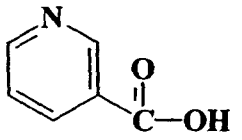
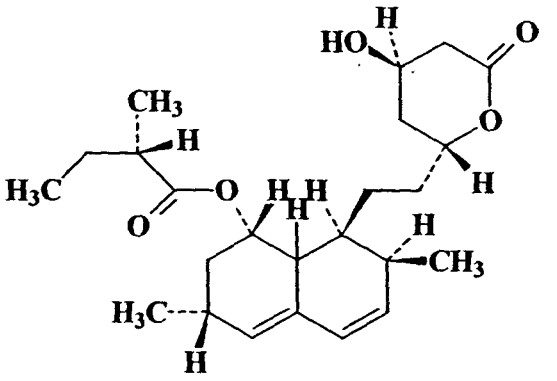
Structure:



NIACIN



LOVASTATIN

FORMULATION: Niaspan® ——— lovastatin, then ——— The tablet strengths are described in this NDA as mg of niacin per tablet followed by mg of lovastatin per tablet. Four different tablets of nicostatin were formulated during clinical development in strengths of 500/10, 500/20, 750/20 and 1000/20. However, only 500/20, 750/20 and 1000/20 tablet strengths are proposed for the commercial use.

Relevant INDs/NDAs/DMFs:
NDA 19-643 (Lovastatin, Merck Sharp and Dohme)
NDA 20-381 (Niacin, KOS Pharmaceuticals Inc.)
IND ——— (Niaspan®); DMF ——— cited for Lovastatin, DMF ——— for Niacin; Various DMF's for ———

Drug Class: Lipid altering agent. Niacin is an antihyperlipidemic agent and vitamin; Lovastatin is total and LDL- cholesterol lowering agent and HMG-CoA reductase Inhibitor.

Indication: Reduction of elevated ——— LDL cholesterol levels, reductions in triglycerides, increases in HDL cholesterol (antidyslipidemic).

Clinical formulation (and components): 500/20, 750/20 and 1000/20 tablet strengths are proposed for the commercial use. The 500/20-mg tablets contain the following active and inactive ingredients:

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COMPOSITION OF NICOSTATIN™ 500/20 TABLETS		
COMPONENT	QUANTITY/TABLET (mg)	%/TABLET
Niacin, USP	500	—
Lovastatin, USP	20	—
Povidone, USP	—	—
HPMC, USP —	—	—
Stearic Acid —	—	—
Polyethylene Glycol —	—	—
HPMC, USP —	—	—
—	—	—
—	—	—
Total	806.90	100

Route of administration: oral
Proposed clinical protocol or use: Nicostatin is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, —— and TG levels, and to increase HDL-cholesterol in subjects with primary hypercholesterolemia and mixed dyslipidemia. The recommended dose is 500/20 to 2000/40 mg once daily at bedtime. Doses greater than 2000/40 mg is not recommended. Women may need lower doses, because data from two nicostatin studies show that LDL-C, HDL-C and TG responses for women were consistently greater than for men.

Introduction and drug history:

The drug nicostatin contains niacin in an extended-release form, and lovastatin, an HMG-CoA reductase inhibitor. Both are currently marketed drugs in USA. Niacin is a B-complex vitamin, antihyperlipidemic agent, and is recommended at doses of 500, 750 and 1000 mg/day. Lovastatin is a cholesterol lowering agent, the initial NDA (NDA 19-643) for this drug was approved on 8/31/1987, and it is recommended at doses of 10, 20, 40 and 80 mg/day.

Studies reviewed within this submission: Since most of the preclinical pharmacology/toxicity studies were submitted in the original application of niacin (NDA 20-381) and lovastatin (NDA 19-643), no new pharm/tox studies were submitted here to support the use of this drug. Sponsor had submitted one pilot PK study in dogs under the IND —— for this drug and the review of this IND is included in appendix 1.

OVERALL SUMMARY AND EVALUATION:

Introduction: The drug nicosatin is a combination of two drugs, niacin and lovastatin. Niacin is a B-complex vitamin. Niacin functions in the body after conversion to nicotinamide adenine dinucleotide (NAD) in the NAD coenzyme system. It lowers elevated total and LDL cholesterol levels, reduces triglycerides, and increases HDL cholesterol. Lovastatin is a cholesterol-lowering drug; it is an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme that catalyzes the rate-limiting step in cholesterol synthesis. Both drugs have been marketed extensively for many years, for oral administration. The proposed doses in combination have been approved for use as the individual agents. Nicostatin with its broad spectrum, has effects on all major lipoprotein classes (LDL-C, HDL-C, TG, ————————. Nicostatin's indication is to lower lipids in individuals with primary hypercholesterolemia and mixed dyslipidemia,

[ ]

Safety Evaluation: There are no preclinical safety studies submitted with this NDA. The sponsor has provided the brief summary of available pharmacology and toxicity of both agents. The combined use of niacin + lovastatin would supposedly provide a beneficial pharmacological effect for the treatment of dyslipidemia. In single dose human PK studies the absorption of niacin and lovastatin from nicostatin appears to be bioequivalent to that with absorption of Niaspan (niacin) and lovastatin.

The toxicities with lovastatin and niacin are briefly summarized in the appended IND review of this drug (in appendix 1).

No studies regarding carcinogenicity, mutagenicity or impairment of fertility with Nicostatin have been conducted. The proposed labeling text under these headings is what is reported under labeling for Niacin and Lovastatin. Niacin given to mice for a lifetime as 1% solution in drinking water (approximately 6-8 times the human dose of 3000 mg/day based on mg/m^2) was not carcinogenic. Niacin was negative in Ames test. No studies on impairment of fertility have been performed with Niacin. Similarly no reproductive toxicity studies have been carried out with Nicostatin or Niacin. It is unknown whether niacin at doses used for lipid disorders can cause fetal harm when administered to pregnant women, or whether it affects reproductive capacity. However, carcinogenicity, mutagenicity or impairment of fertility and repro-tox studies have been conducted with lovastatin, and are indicated as pregnancy category X in the label for lovastatin (also in nicostatin label). Lovastatin carcinogenicity studies have indicated increased incidence of hepatocelluar carcinomas and adenomas, pulmonary adenomas, papilloma of non-glandular stomach mucosa, and thyroid neoplasm. Lovastatin is not mutagenic.

Labeling Review: In general, no new preclinical sections of label for nicostatin have been provided. The label for nicostatin include approved labels from niacin and lovastatin. However, the following changes in labeling are recommended:

1.Under the headings 'Pregnancy and lactation'

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, Nicostatin is contraindicated ——— in women who are or may become pregnant and in lactating ——— mothers. Nicostatin may cause fetal harm when administered to pregnant women. NICOSTATIN 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, NICOSTATIN should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus (see PRECAUTIONS, Pregnancy).

2. Under the heading **Pregnancy**, 'Pregnancy Category X — See CONTRAINDICATIONS'

Niacin:
Animal reproduction studies have not been conducted with Niacin or with NICOSTATIN. 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 nicostatin for primary hypercholesterolemia (Types IIa or IIb) becomes pregnant, the drug should be discontinued. ———

Justification for the changes: The above statement is in the approved niacin label and should be stated in the current label under 'Niacin'.

3. Under 'Mechanism of action of niacin', the ——— should be deleted from the label.

Mechanism of Action
Niacin

The mechanism by which niacin alters lipid profiles 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. [ ]

[ ]

Internal comments: Since both are approved drugs, their safety profile has been individually well characterized, and is used at approved doses, the approval (AP) of this application is recommended.

External Recommendation: From the preclinical standpoint, approval of this application is recommended, pending labeling changes.

Indra Antonipillai, Ph.D.
Pharmacologist, HFD-510

cc: NDA Arch
HFD510
HFD510/antonipillai/davisbruno/parks/pariser/koch
Filename: nda21249

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ON ORIGINAL

Appendix 1:
IND ——— **Review Completed: June 10, 1998**

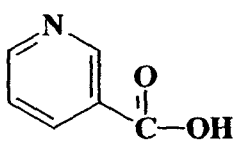
Sponsor: Kos Pharmaceuticals, Inc; Miami, FL 33131

Date Submitted: May 26, 1998 **Date Received: May 28, 1998**

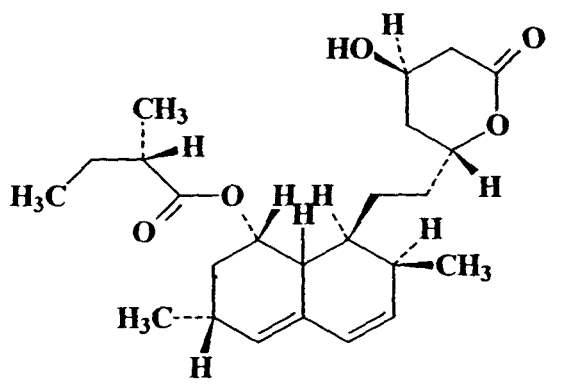
PHARMACOLOGY REVIEW OF INITIAL IND SUBMISSION
Amendment to IND ——— Serial #000 (May 26,1998)

DRUG: Nicostatin, combination of Lovastatin and Niacin, extended release

STRUCTURAL FORMULA: Product consists of a niacin (nicotinic acid) ——— (Niaspan®) ——— Lovastatin. (500 mg Niacin/ — mg Lovastatin)
Nicotinic acid: $C_6H_5NO_2$; MW 123.11, pyridine-3-carboxylic acid, niacin
Lovastatin: $C_{24}H_{36}O_5$; MW 404.55; mevinolin, monacolinK, 6α methyl compactin.



NIACIN



LOVASTATIN

FORMULATION: Niaspan® ——— lovastatin, ——— ——— Niaspan® ——— come in strengths of — 500, 750 and 1000 mg. ——— Lovastatin is currently labeled for 10-80 mg dosages.

COMPOSITION OF NICOSTATIN™ 500 — TABLETS		
COMPONENT	QUANTITY/TABLET (mg)	%/TABLET
Niacin, USP	500	
Lovastatin, USP		
Povidone, USP		
HPMC, USP		
Stearic Acid, NF		
Polyethylene Glycol — NF		
HPMC, USP		
Total	806.86	100

CATEGORY: Lipid altering agent. Niacin is an antihyperlipidemic agent and vitamin; Lovastatin is an antihyperlipidemic agent (HMG-CoA Reductase Inhibitor)

INDICATION: Reduction of elevated total and LDL cholesterol levels, reductions in triglycerides, increases in HDL cholesterol (antidyslipidemic).

RELATED IND: NDA 20-381 (Niaspan®); IND —— (Niaspan®); DMF —— cited for Lovastatin, DMF —— for Niacin; Various DMF's for ——————

MEMOS: Pre-IND meeting held 6/3/97; minutes included in package. There was little discussion on pharmacology at the meeting. Since both products are approved, it was thought that literature citations would be sufficient for pharmacology.

CLINICAL STATUS: Phase I: Two protocols proposed:
Protocol 97/07: "A Pilot Study of the Comparative Bioavailability of a Niaspan® and Lovastatin Combination Tablet versus Co-administration of Niaspan® and Mevacor®". Single-dose study in male and female healthy volunteers comparing the bioavailability of lovastatin and niacin from three Nicostatin™ 500/10 tablets versus co-administration of three 10 mg lovastatin (Mevacor®) tablets and three 500 mg Niaspan® tablets. Primary variables for niacin are urine recovery of niacin and nicotinuric acid combined. Primary variables for lovastatin are C_{max} and AUC(0-last and 0-∞). Scheduled to start in July 1988.

Protocol MA-98-010407: "A Long-Term, Open-Label, Multi-Center Trial of the Safety and Efficacy of Nicostatin™in Patients with Dyslipidemia." Men and women ≥21 years old. Patients will undergo a 4-month forced dose-escalation period receiving total doses of 500 mg niacin and 10 mg lovastatin, 1000 mg niacin and 20 mg lovastatin , 1500 mg niacin and 30 mg lovastatin and 2000 mg niacin and 40 mg lovastatin for one month each. Nicostatin™ will be administered daily at bedtime after a low-fat snack. Primary endpoints are change from baseline in LDL-C and HDL-C. Secondary endpoints are: Total cholesterol, VLDL-C, TG and ratio of TC to HDL-C, ratio of LDL-C to HDL-C, Apolipoprotein A-I, Apolipoprotein B and the LP-AI and LP AI-AII content of the HDL particles, Lp(a). Scheduled to start in 1998 (enrollment in 9/88).

[ ]

ANTICIPATED SPECIAL RISKS: Since doses are going to be lower than levels are currently approved, there would appear to be no specific concerns beyond those which have already been outlined during the approval process for Niaspan® and Mevacor®. However, according to the sponsor, rhabdomyolysis has been reported in treatments with combinations of nicotinic acid and statins. This information is included in the investigator's brochure.

PREVIOUS HUMAN EXPERIENCE: There exist published studies which have reported effects with combinations of nicotinic acid and various statins. In 8 patients taking Niaspan® and lovastatin, there was an enhanced TC, LDL-C and TG response. This was

also true for the other statin combinations with Niaspan®. Incidence of elevated LFT's was <1% after a mean treatment duration of 56 weeks. Dose of Niaspan® was 2000 mg, statins ranged from 10-20 mg. Thus, these exposures represent lower exposure to statins compared to what the sponsor proposes.

SUMMARY OF PHARMACOLOGY AND TOXICOLOGY

No sponsor-generated data on this formulation was provided in this submission. The safety profile of both agents individually have been well characterized. The sponsor provided a brief summary of the available information related to the pharmacology and toxicology of these agents.

NIACIN PHARMACOLOGY

Primary effects appears to be decreased production of VLDL-C which may be due in part to a transient inhibitory effect of nicotinic acid on lipolysis, a decreased delivery of FFA's to the liver and a decrease in TG synthesis and VLDL-TG transport. Enhanced clearance of VLDL-C may also occur, possibly related to enhanced lipoprotein lipase. The mechanism to raise HDL-C is not clear, but may be related to a decreased clearance of apo A-I and a decreased synthesis of apo A-II. Nicotinic acid does not alter the rates of cholesterol synthesis or bile acid excretion.

Niacin is metabolized differently in different species; there is no perfect animal model for humans. The rabbit appears to be the best model for studying antihyperlipidemic and anti-atherosclerotic effects.

LOVASTATIN PHARMACOLOGY

Lovastatin is a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase. Therefore, lovastatin inhibits a key rate-limiting step in cholesterol biosynthesis. Lovastatin is actually a pro-drug lactone form which is inactive. After absorption, the lactone ring is hydrolyzed to form the β-hydroxyacid, the active form. Lovastatin reduced both normal and elevated LDL-C concentrations. This is primarily due to a decrease in LDL particle number, although there is also a slight decrease in cholesterol content of the LDL particle and a small decrease in VLDL-C possibly due to hepatic secretion. TG declines, reflecting the decrease in VLDL-C levels. A modest increase in HDL-C occurs, but they do not appear to lower Lp(a) levels.

NIACIN TOXICOLOGY

Primary information on niacin toxicity has relied on extensive experience in humans. Most studies are very old. 1 g/kg was well tolerated in mice; some animals died at 3 g/kg. Similar findings were found with I.V. administration of 1 g/kg in rats. In dogs, 2 g/kg were well tolerated.

LD_{50}:
~ 4500 mg/kg for mice
~3500 mg/kg in rats and guinea pigs.

Death was preceded by clonic convulsions at lethal or near-lethal doses. Animals either died or recovered without apparent lasting effects.

Few studies are available on multiple dose toxicity of niacin. There some effects that are inconsistent. Some studies report 0.1-2% niacin administered in the diet produced fatty livers, while other experiments did not confirm this. In dogs, some studies report weight loss, bloody feces, convulsions and death with related gastrointestinal erosions and CNS effects; other studies show no toxicity. In one study, dogs administered 100 mg/kg/day for 8 and 32 months resulted in weight loss. However, none of the studies described were standard toxicology studies.

There is no information on reproductive or carcinogenicity studies with niacin.

LOVASTATIN TOXICITY

Liver is the primary target organ for lovastatin action. Effects may vary in differences and ranged from no change in primates to subtle transient elevations of LFT's in dogs with morphological changes in rodent liver to frank hepatocellular necrosis in the rabbit.

Optic nerve degeneration was detected in dogs starting at 60 mg/kg/day (estimated 30X human exposure based on drug levels). Vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis were also seen in dogs treated at 180 mg/kg for 14 weeks. CNS vascular lesions were seen in dogs at 180 mg/kg. This appears to be a class effects.

Cataracts were seen in dogs treated for 11 and 28 weeks at 180 and 1 year at 60 mg/kg.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation were seen in dogs receiving oral lovastatin at 20 mg/kg/day in a 1 year study. No drug-related effects were noted on fertility although there were decreased fertility in one of two studies in male rats with another HMG-CoA Reductase Inhibitor.

Statins have been class-labeled with a Class X for pregnancy.

PHARMACOKINETICS AND METABOLISM

In a pilot PK study in beagle dogs, the relative bioavailability of lovastatin was compared in Nicostatin™ (the combined product) and Mevacor® (lovastatin alone) and Niaspan® (niacin alone). In a randomized crossover experiment, 12 dogs received:

1. 1000 mg Nicostatin™ (two tablets total 20 mg lovastatin)
2. Niaspan® 500 mg tablets plus two Mevacor® 10 mg tablets.

Doses were administered at least 14 days apart. Only lovastatin was measured in this experiment. Plasma profiles indicate similar absorption from both formulations, even though the dissolution profiles *in vitro* are different. Nicostatin™ tablets were —% and ~ % dissolved at 30 and 45 min, while Mevacor® tablets were — and —% dissolved at 30 and 45 minutes respectively. Despite slower lovastatin dissolution in Nicostatin™, the average peak serum concentrations in dogs were similar between Nicostatin™ and Mevacor®

SUMMARY AND EVALUATION

No sponsor-generated data on this formulation was provided in this submission except for results from a small pilot PK study in dogs. The safety profile of both agents individually have been well characterized. The sponsor provided a brief summary of the available information related to the pharmacology and toxicology of these agents. The proposed use represents use in combination of doses that have been approved for use as the individual agents. The sponsor appears to be aware of the potential toxicities of these agents. At the current time, no further preclinical pharmacology studies are necessary to initiate the proposed studies. However, if human PK data indicate that PK parameters change significantly compared to the approved formulations, a bridging study in animals may be necessary.

TO BE COMMUNICATED TO SPONSOR

No new preclinical data are required to initiate the proposed studies with Nicostatin™. However, if human PK analyses indicate important changes in the PK of the combined products, a bridging toxicology study with the combination formulation may be recommended.

Ronald W. Steigerwalt, Ph.D.
Pharmacology Team Leader

cc: IND Arch
HFD510
HFD510/Steigerwalt/Simoneau
Review Code: SA

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Addendum to the Pharmacologist's June 5, 2001 review of NDA 21-249

Labeling Changes: Following labeling changes have been made, after completion of the pharmacology review (dated June 5, 2001):

1.Under the heading 'Pregnancy and lactation' the following recommended change from KOS Pharmaceuticals (submitted on 6/18/2001) was acceptable

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).

2. Under the heading **Pregnancy**, 'Pregnancy Category X — See CONTRAINDICATIONS', the following sentence that ——— , was deleted

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.

Justification for the changes: The above statement in the ADVICOR label should be deleted, because ADVICOR ———

Indra Antonipillai, Ph.D.
Pharmacologist, HFD-510

cc: NDA Arch
HFD510
HFD510/antonipillai/davisbruno/parks/pariser/koch
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/s/

Indra Antonipillai
7/12/01 01:43:32 PM
PHARMACOLOGIST
The labeling comments have already been communicated to the sponsor

Karen Davis-Bruno
7/16/01 04:37:37 PM
PHARMACOLOGIST