CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-249

MEDICAL REVIEW(S)

MEDICAL TEAMLEADER'S MEMO ON NEW DRUG APPLICATION

NDA #: 21-249
Product: Advicor (combination tablet of Niaspan and lovastatin)
Sponsor: Kos Pharmaceuticals
Date of Submission: September 25, 2000

Primary Medical Reviewer: Anne Pariser, MD
Statistical Reviewer: Joy Mele, MS

BACKGROUND

Combination drug products have been reviewed and approved by the Agency for a variety of conditions such as hypertension, contraception, and more recently, diabetes mellitus. The rationale behind the development of a combination drug product can be for improved efficacy over the individual components (e.g., glucophage plus glyburide), dose-sparing, or counterbalancing a specific drug adverse effect (e.g. triamterene plus hydrochlorothiazide or estrogen/progestins).

The sponsor's rationale for developing Advicor was to provide improved LDL-lowering over the individual components, niaspan and lovastatin. In addition, the combination product would have TG-lowering and HDL-raising effects. The clinical development program was designed to evaluate Advicor's efficacy in patients with primary hypercholesterolemia (Types IIa) and mixed dyslipidemia (Types IIb) whose primary lipid derangement was an elevated LDL-C level. Patients were selected if their screening LDL-C levels were not at NCEP goals (based on the 1993 published guidelines). The indications sought include consideration of Advicor as initial therapy for LDL-lowering in these types of patients.

Due to poor tolerability associated with niacin-containing products, these drugs must be initiated at the lowest, less-efficacious doses for titration purposes only. This drawback of niacin dosing led the sponsor to conduct forced-titration clinical studies involving not only the niacin and Advicor treatment groups but also the lovastatin comparator arm. This study design was criticized by the FDA statistician during pre-NDA discussions with the sponsor since the higher drop-out rate in the niaspan and Advicor arms might result in noncomparable treatment groups beyond the first titration phase. This concern is particularly relevant if drop-outs were due to lack of efficacy. To account for the effect of discontinuations on efficacy, analyses were performed by the statistician on evaluable cases (observed cases) and intent-to-treat population with last observations carried forward (LOCF).

The proposed Advicor tablets contained the following amount of niaspan/lovastatin: 500/20, 750/20, and 1000/20. These three tablets would allow for Advicor dosing at 500/20, 750/20, 1000/20, 1000/40, 1500/40, and 2000/40 strengths. Consideration for approval of this product as an LDL-lowering agent as proposed by the sponsor would require that Advicor, at each of its possible dosing schemes, have improved LDL-lowering efficacy over niaspan and lovastatin monotherapy.

Although the study population was not specifically selected for elevated TGs or decreased HDL-C levels, the Division also reviewed the effects of Advicor on TG-lowering and HDL-raising compared to niaspan and lovastatin monotherapy.

CLINICAL DATA SUBMITTED

The sponsor submitted data from two double-blind, active-control clinical trials (MA-98-010414 and 98-010406) to support their proposed efficacy claims. These studies evaluated different dosage strengths of Advicor to its individual components, niaspan and lovastatin, during a 20- (Study MA-14) and 28-week (Study MA-06) treatment period. Patients completing these studies were offered enrollment into a 48-week, open-label extension phase (Study MA-09). In addition, an open-label, uncontrolled, 52-week study of Advicor (Study MA-07) was submitted to NDA 21-249. Since both studies MA-09 and MA-07 contain no comparative efficacy data, these results were considered primarily in the evaluation of Advicor's long-term safety and tolerability; however, the durability of the lipid-altering efficacy was also addressed by the primary reviewer.

EFFICACY RESULTS

Initial Therapy for LDL-C Lowering

Study MA-14

As stated earlier, the combination of niaspan and lovastatin (as Advicor) for purposes of LDL-lowering must demonstrate a greater LDL-lowering than the individual agents as monotherapy. From the table below, obtained from Dr. Pariser's review, it is evident that Study MA-14 has significant problems in that valid comparative efficacy analyses between niaspan and lovastatin to the proposed dosage strengths of Advicor cannot be performed. Specifically, none of the to-be-marketed strengths could be compared with their individual components at the same timepoint.

MA-14 Advicor vs Lovastatin Valid Comparisons (bolded)

	Week				
Treatment	**4**	**8**	**12**	**16**	**20**
Niaspan (mg)	**500**	**1000**	**1500**	**2000**	**2500**
Advicor/10 (mg/mg)	**500/10**	**1000/10**	1500/10	2000/10	2500/10
Advicor/20 (mg/mg)	500/20	1000/20	**1500/20**	**2000/20**	2500/20
Advicor/40 (mg/mg)	500/40	1000/40	1500/40	2000/40	**2500/40**
Lovastatin (mg)	**10**	**10**	**20**	**20**	**40**

Although the sponsor concluded that doses of Advicor 1500/20, 2000/20, and 2500/40 achieved significantly greater LDL-lowering than lovastatin or niaspan monotherapy, none of these dosage strengths can be attained with the proposed marketed strengths of 500/20, 750/20, and 1000/20.

Dr. Pariser and Ms. Mele each raised concerns regarding the LDL-lowering achieved in the lovastatin treatment arm in Study MA-14. Each reviewer noted the flat response with lovastatin monotherapy despite the doubling of its dose (see Figure 1, page 41 of Dr. Pariser's review) which would typically result in an additional 5 to 6% LDL-lowering. In contrast, the LDL-lowering of Advicor 500/10, 500/20, and 500/40 showed the expected progressive LDL-lowering consistent with a doubling of the lovastatin component. Indeed, the –24% reduction observed with lovastatin 40 mg monotherapy in Study MA-

14 is 6 to 9% lower than historical data obtained from trials using the innovator product, Mevacor.

MA-14 Mean % Change LDL, Comparisons of MA-14 vs Mevacor (obtained from Dr. Pariser's review)

	Mean % Change LDL			
Lovastatin Dose	Mevacor Label	*EXCEL	*Lova-Prava Study	Lovastatin Control Group
10 mg	-21 %	NA	NA	-19%
20 mg	-27%	-24%	-28%	-22%
40 mg	-31%	-30%	-33%	-24%

*see Dr. Pariser's review for references

In conclusion, the poor LDL-lowering of lovastatin monotherapy in Study MA-14 was inconsistent with both the known efficacy data for Mevacor and the lovastatin component of Advicor. These findings, along with the absence of valid comparative efficacy data for the to-be-marketed Advicor dosage strengths, do not allow for the consideration of MA-14 efficacy results in the review of this application.

Study MA-06

By contrast, Study MA-06 employed a study design which allowed for valid comparisons of proposed Advicor doses to niaspan and lovastatin monotherapy (see Table below). Furthermore, the LDL-lowering response of the lovastatin arm was consistent with historical data.

MA-06 Advicor vs Lovastatin Valid Comparisons (bolded)

	Weeks						
Treatment	**4**	**8**	**12**	**16**	**20**	**24**	**28**
Nico/20 (mg/mg)	**500/20**	**750/20**	**1000/20**	1000/20	1000/20	1000/20	1000/20
Nico/40(mg/mg)	**500/20**	**750/20**	**1000/20**	**1000/40**	**1500/40**	**2000/40**	**2000/40**
Niaspan (mg)	**500**	**750**	**1000**	**1000**	**1500**	**2000**	**2000**
Lovastatin (mg)	**20**	**20**	**20**	**40**	**40**	**40**	**40**

Review of the LDL-lowering effect of these treatments revealed that Advicor achieved greater LDL-lowering than any dose of niaspan tested but failed to show any advantage over lovastatin monotherapy except at its highest recommended dose of 2000/40(see table below adapted from Ms. Mele's review). The LDL-lowering response at Week 28 was also evaluated in the observed cases by the statistician and similar results to the ITT population were obtained.

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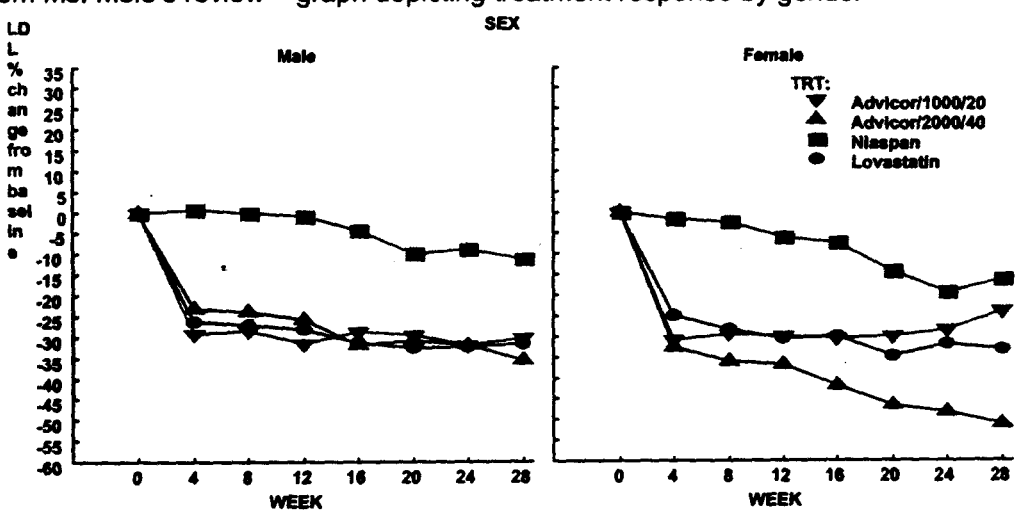
ON ORIGINAL

ITT (LOCF) LDL-C Lowering Responses in Study 406

	Advicor mean (SD)	Niaspan mean (SD)	Lovastatin mean (SD)	Nico vs Nia p-value	Nico vs Lova p-value
Dose at Wk 4 % LDL chg	500/20 -29% (11)	500 -5% (11)	20 -26% (10)	0.0001	0.13
Dose at Wk 8 % LDL chg	750/20 -29% (12)	750 -1% (12)	20 -27% (10)	0.0001	0.52
Dose at Wk 12 % LDL chg	1000/20 -30% (13)	1000 -3% (12)	20 -29% (9)	0.0001	0.49
Dose at Wk 16 % LDL chg	1000/40 -35% (13)	1000 -5% (13)	40 -31% (10)	0.0001	0.06
Dose at Wk 20 % LDL chg	1500/40 -36% (16)	1500 -10% (13)	40 -33% (10)	0.0001	0.20
Dose at Wk 24 % LDL chg	2000/40 -37% (18)	2000 -11% (15)	40 -31% (10)	0.0001	0.04
Dose at Wk 28 % LDL chg	2000/40 -40% (14)	2000 -10% (15)	40 -31% (11)	0.0001	0.002

The statistical reviewer also evaluated the LDL-lowering response in each treatment group by gender. There was no appreciable difference in LDL-lowering with lovastatin versus Advicor in males whereas females had a greater response to Advicor for LDL-lowering than with lovastatin. The LDL-lowering in males treated with Advicor was –34% versus –31% in the male lovastatin group. In contrast, females treated with Advicor achieved a –47% LDL-C reduction at study endpoint compared to –31% in the female lovastatin group. This pattern was observed at all doses of Advicor throughout this 28-week study (see Figure below). In effect, the greater LDL-lowering efficacy of Advicor 2000/40 versus lovastatin 40 mg was confined only to female patients.

From Ms. Mele's review – graph depicting treatment response by gender



The evaluation of Advicor as an initial therapy for LDL-lowering reveals many limitations. From Study MA-06 it is evident that an advantage of combined therapy over lovastatin monotherapy is only observed at the highest dose of Advicor 2000/40. This will only be

achieved after 24 weeks of forced-titration due to poor tolerability related to the niaspan component. Furthermore, men achieved no additional LDL-lowering benefit with the addition of niaspan to lovastatin. Finally, the greater LDL-lowering observed with Advicor 2000/40 over lovastatin monotherapy did not consider the efficacy of lovastatin at its highest approved dose of 80 mg. Although this dose was not studied it is conceivable that individuals already on lovastatin as their first-line therapy for elevated LDL-C can achieve a similar response to combination therapy with niaspan by titrating to lovastatin 80 mg. The sponsor's argument that Advicor 2000/40 was dose-sparing for the muscle and liver problems associated with high dose statin therapy was unfounded since these adverse events have been reported with combination therapy as well as monotherapy. Overall, the valid efficacy data (i.e. Study MA-06) reviewed do not support the use of Advicor as initial therapy for patients requiring primarily LDL-C reduction.

Combined Therapy for Multiple Dyslipidemias

Since the review of this application failed to support the primary indication sought (i.e. initial therapy for LDL-lowering), the lipid-lowering efficacy of the individual components of Advicor was evaluated for its effects on LDL-C, TG, and HDL-C levels. In this setting, Advicor would provide an advantage over lovastatin monotherapy for HDL-raising and TG-lowering and an advantage over niaspan for LDL-lowering. From the LDL-lowering efficacy results of Study MA-06, it has already been summarized that Advicor provides an advantage over niaspan monotherapy for LDL-lowering at all marketed strengths of niaspan.

Again, Study MA-06 is only considered in this efficacy analysis since it provides lipid-altering data for the proposed dosage strengths of Advicor.

HDL-raising

Advicor demonstrated dose-related changes in HDL-C from +11 to +28% over the 28-week treatment period of Study MA-06. These results were significantly greater than those achieved with either niaspan or lovastatin at any dose studied.

TG-lowering

From Study MA-06, Advicor achieved significantly greater TG-lowering than niaspan at doses of 750/20 and greater and lovastatin at doses of 1000/20 and greater.

The following table (adapted from Ms. Mele's review) summarizes the HDL-raising and TG-lowering effect of Advicor compared to its individual components.

Advicor vs. Niaspan and Lovastatin for HDL and TG Response

	Advicor Mean (SD)	Niaspan Mean (SD)	Lovastatin Mean (SD)	NIC Vs NIA p-value	NIC Vs LOVA p-value
Dose at Week 4	500/20	500	20		
HDL%change	+11% (11)	+5% (11)	+6% (10)	.007	.005
TG%change	-16% (32)	-8% (29)	-16% (23)	.15	.89
Dose at Week 8	750/20	750	20		
HDL%change	+14% (14)	+6% (14)	+3% (12)	.002	.0001
TG%change	-21% (30)	-5% (37)	-16% (28)	.002	.26

	Advicor Mean (SD)	Niaspan Mean (SD)	Lovastatin Mean (SD)	NIC Vs NIA p-value	NIC Vs LOVA p-value
Dose at Wk 12	1000/20	1000	20		
HDL%change	+19% (15)	+12% (14)	+3% (10)	.001	.0001
TG%change	-26% (28)	-13% (33)	-15% (26)	.01	.01
Dose Wk 16	1000/40	1000	40		
HDL%change	+19% (14)	+12% (16)	+5% (11)	.02	.0001
TG%change	-32% (30)	-18% (27)	-15% (23)	.04	.01
Dose at Wk 20	1500/40	1500	40		
HDL%change	+26% (15)	+18% (19)	+5% (12)	.007	.0001
TG%change	-37% (32)	-22% (31)	-18% (22)	.01	.0006
Dose at Wk 24	2000/40	2000	40		
HDL%change	+28% (18)	+20% (17)	+5% (12)	.006	.0001
TG%change	-43% (27)	-30% (26)	-16% (23)	.11	.0007
Dose at Wk 28	2000/40	2000	40		
HDL%change	+28% (17)	+19% (21)	+6% (15)	.0008	.0001
TG%change	-40% (27)	-20% (32)	-20% (22)	.004	.0002

In conclusion, study MA-06 provides evidence that the combination of niaspan with lovastatin is a convenient drug formulation for individuals requiring additional treatment of multiple lipid derangements not adequately treated with a single agent.

SAFETY AND TOLERABILITY RESULTS

As summarized in Dr. Pariser's review, both lovastatin and niacin are approved products for the treatment of dyslipidemias with extensive safety data. The most significant safety concerns associated with these products include skeletal muscle and liver toxicity.

Muscle toxicity manifested as myalgias with elevated CK levels, which rarely progress to rhabdomyolysis with acute renal failure, have been reported with lovastatin (and other statins). In long-term placebo-controlled trials involving Mevacor, the incidence of myopathy (myalgias with CK levels ≥ 10X ULN) is less than 0.2% across its entire dosage range. The exact mechanism by which this adverse event (AE) occurs is unknown but risk factors which may alter drug levels (e.g., CYP3A4 inhibitors) and individual susceptibilities (e.g., age, renal impairment) may have a causal role in development of this AE. The combined use of lipid-altering drugs, such as niacin, fibrates, and statins, have also been reported to increase the risk of myopathy and rhabdomyolysis via a proposed pharmacodynamic rather than a pharmacokinetic interaction. These cases are rarely, if ever, observed in clinical trials due to the small number of patients studied and the short duration of investigation which limit the ability to detect an uncommon AE.

Similarly, clinically significant liver toxicities with both these agents are rarely reported in lipid-altering trials of short duration. Detection of clinically relevant increases in hepatic transaminases provide a crude estimate of the drugs' effects on the liver but are unrevealing for the incidence of serious hepatic injuries such as hepatitis, hepatic necrosis and failure. The incidence of consecutive > 3x ULN elevations of hepatic transaminases have been reported at 0.9% for lovastatin 40 mg and 1.0% for niaspan.

Lovastatin is generally well-tolerated with discontinuation rates due to AEs similar to that of placebo in controlled studies. In contrast, niacin-containing products are poorly tolerated with the most common side effects being flushing, pruritus, and GI disturbances.

The clinical studies reviewed in this NDA provide up to 76 weeks of safety and tolerability data for Advicor. Twenty to 28-weeks of these data were from active-controlled studies (Study MA-14 and MA-06) while the remainder of the safety data were from open-label, uncontrolled studies (MA-09 and MA-07).

Few patients experienced clinically significant increases in hepatic transaminases (> 3x ULN). In the two active-control trials there was a 1 to 2% incidence of significant ALT/AST increases involving both Advicor and lovastatin treatment groups. All these cases either resolved while continuing therapy or normalized with drug discontinuation/interruption.

There were no cases of rhabdomyolysis in these studies. One patient developed myopathy in the Advicor open-label study while receiving a dose of 2000/40. Study medication was discontinued and symptoms resolved and CK levels returned to normal.

The active-control trials reveal more patients in the Advicor and niaspan treatment arms (84-97%) reporting AEs compared to the lovastatin treatment group (73-80%). Flushing accounted for the majority of these AEs in the niacin/Advicor groups (53-83%) versus lovastatin (15-20%). Pruritus was also more common in the niacin/Advicor groups (3-11%) versus only 2-3% in the lovastatin group. More patients receiving either niaspan or Advicor discontinued therapy (approximately 30%) due to AEs compared to the lovastatin group (12-13%). In the open-label extension studies, the discontinuation rate continued with 32% of the patients continuing in the 1-year open label phase discontinuing treatment with Advicor.

Niacin therapy is associated with increased fasting blood sugars (FBS) and worsening glucose control in diabetics. FBS elevations occurred in 53-65% of the Advicor/niaspan-treated patients versus 24-41% of the lovastatin treated patients. Other laboratory abnormalities associated with niacin include hypophosphatemia, decreases in platelet counts, and increases in prothombin time. These findings were also observed with Advicor therapy.

Overall, the safety and tolerability of lovastatin and niaspan established in controlled trials are reflected in their combined use as Advicor. The studies reviewed by Dr. Pariser show a similar safety profile for the combination product versus its individual components albeit these studies are not designed to detect the rare serious AEs such as rhabdomyolysis and liver damage. Advicor (and niaspan) is poorly tolerated compared to lovastatin with AEs such as flushing and pruritus resulting in approximately one-third of patients discontinuing medication. This finding reflects a limitation of Advicor (and niaspan) as a drug intended for chronic treatment of dyslipidemia.

PROPOSED LABELING

Dr. Pariser's review of the sponsor's submitted labeling provides an in-depth summary of the clinical trials, proposed indications, and safety issues. Overall, the sponsor seeks to receive approval for Advicor as a first-line agent for the treatment of elevated LDL-C,

citing greater efficacy with Advicor over lovastatin monotherapy. In addition, the sponsor proposes to merge both drug labels with respect to their clinical studies (in particular, clinical endpoint trials) and unique indications of the individual components.

COMMENTS ON LABELING PROPOSALS

Clinical Data from Niaspan and Lovastatin

The sponsor has proposed to incorporate the clinical study results and

Perhaps more relevant to the FDA review process however, is the promotional potential of these claims. The inclusion of these clinical studies in the Advicor label allows for the implied claim of clinical benefit that has yet to be demonstrated. As a result, the Advicor label should not include any clinical outcome data or indications for which both lovastatin and niaspan do not have in common.

Indications

There is no basis for using Advicor as initial therapy for the management of patients with elevated LDL-C levels. The addition of niaspan to lovastatin did not provide any greater LDL-lowering than lovastatin monotherapy except at the highest dose of Advicor 2000/40. Although not evaluated, it is conceivable that monotherapy with lovastatin 80 mg would afford a similar LDL-reduction to that of the maximum Advicor dose. Furthermore, the greater LDL-lowering effect of Advicor 2000/40 over lovastatin 40 mg was observed only in female patients. Given the Advicor's limited efficacy and poor tolerability resulting in greater discontinuation of therapy, there is no apparent advantage of Advicor over lovastatin monotherapy or other available statins with greater LDL-lowering efficacy as a first-line agent.

The addition of niacin to a statin has been recommended in clinical practice for the management of mixed dyslipidemias provided that the risks of combined therapy are adequately monitored and do not outweigh the benefits. In this setting, clinicians take

advantage of the LDL-lowering efficacy of the statin and the TG-lowering and HDL-raising efficacy of niacin. Although the sponsor did not develop their clinical program with the intention of targeting patients with mixed dyslipidemia by studying specifically Types IIb or — dyslipidemics, the medical and statistical reviews conclude that there is sufficient evidence to support the combination of niaspan and lovastatin as a convenient, combination product for the management of multiple lipid derangements.

The rationale for such an indication is based on the observation that atherogenic lipoprotein particles are confined not only to the cholesterol-rich LDL particle but also to the TG-rich lipoproteins. Patients with elevated triglycerides often have associated findings of low HDL-C levels, hypertension, glucose intolerance, and obesity. The identification of triglycerides as a risk component in CVD has shifted the focus of drug intervention from solely LDL-C lowering to both lowering LDL-C and TG levels (and HDL-raising) in certain patient populations. Indeed, many clinical cardiovascular events occur in individuals with average LDL-C levels but have elevated TG levels and low HDL-C levels.

In the most recently published National Cholesterol Education Program (ATP III) guidelines, attention was given to the management of the *metabolic syndrome* with its mixed dyslipidemia presentation. Under these circumstances, non-HDL-C levels (the atherogenic LDL-C and VLDL-C particles) are considered secondary targets of therapy for individuals identified with TG levels exceeding 200 mg/dL. The primary goal of therapy still, however, remains the LDL-C level. Once achieving the desired LDL-C goal, the non-HDL-C goal should be managed first with maximal doses of an LDL-lowering drug. The addition of niacin or a fibrate is recommended only if the lipid goals (i.e., LDL-C and non-HDL goals) cannot be reached. This management approach considers the benefits and risks of combination lipid-altering therapy. Although there is an expected benefit associated with treating elevated LDL-C and TG levels and decreased HDL-C levels, there is a risk of myopathy and liver injury associated with combined drug therapy. Unless a combination product provides improved efficacy and is dose-sparing for toxicity or has adequate safety data to address the rare serious AEs, treatment of dyslipidemias should first be managed by optimizing the single agent.

The lipid-altering efficacy of Advicor does not reduce the dose of the individual components. In particular, to achieve a greater LDL-lowering over lovastatin monotherapy the highest dose of niaspan is still required in the 2000/40 combination tablet. Furthermore, this clinical application does not provide adequate safety data to definitively conclude the safety of Advicor over statin or niaspan monotherapy. As such, it is appropriate to approve Advicor as a second line agent for the management of mixed dyslipidemias.

RECOMMENDATIONS

Pending labeling negotiations, this application should be approved as a second-line combination product in patients with Types IIa and IIb dyslipidemia requiring further management of their dyslipidemias not adequately controlled with lovastatin or niaspan monotherapy.

Mary H. Parks, MD
Medical Team Leader

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/s/

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APPEARS THIS WAY
ON ORIGINAL

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #: 21-249	**Application Type:** NDA 505(b)(2)
Sponsor: Kos Pharmaceuticals, Inc.	**Proprietary Name:** Advicor
Investigator: Multiple (Not named)	**USAN Name:** Niacin extended-release and lovastatin tablets
Category: Lipid-altering drug	**Route of Administration:** Oral
Reviewer: Anne R. Pariser, M.D.	**Review Date:** 22-Jul-2001

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
21-Sep-2000	22-Sep-2000	4S	

RELATED APPLICATIONS (If applicable)

Document Date	Application Type	Comments

REVIEW SUMMARY: The NDA was submitted for the approval of Advicor (niacin extended-release/lovastatin in combination) as a lipid-altering agent. The Advicor clinical program sought to demonstrate the efficacy of combination therapy with niacin extended-release and lovastatin on multiple lipid parameters, particularly LDL-C, and to demonstrate Advicor's safety and efficacy for chronic administration. The Sponsor's main goal for the NDA submission was that combination therapy with niacin extended–release and lovastatin (as Advicor) be approved for first-line treatment of hypercholesterolemia. The Sponsor submitted twelve studies to this application: Six pharmacokinetic studies, four clinical safety and efficacy studies, and two safety extension studies.

The results of these studies do not support the proposed indication because:

1) Advicor at doses lower than 2000/40 provided no greater LDL-lowering advantage over lovastatin monotherapy; and
2) The greater LDL-lowering efficacy of Advicor 2000/40 was confined only to female patients.

The efficacy results, however, do support Advicor as a convenient product for patients who require treatment of elevated cholesterol and triglyceride levels and low HDL-C levels that are not effectively treated with single agent therapy.

OUTSTANDING ISSUES:

RECOMMENDED REGULATORY ACTION: N drive location:

New clinical studies	_____	**Clinical Hold**	_____ **Study May Proceed**
NDA, Efficacy/Label supplement:	XX	**Approvable**	___ **Not Approvable**

SIGNATURES Medical Reviewer: **Date:**

Medical Team Leader: **Date:**

Table of Contents

I. Executive Summary

A. Recommendations

The data from the clinical safety and efficacy studies submitted to NDA 21-249 do not support the Sponsor's proposed indication of Advicor as a first-line drug treatment for low density lipoprotein (LDL) lowering, and it is recommended that Advicor not receive approval for this indication.

There were two controlled clinical studies, MA-14 and MA-06, submitted to the NDA. The review of MA-14 raised several problems with the study that made the efficacy results uninterpretable and non-supportive of the proposed label. The MA-06 review showed that significantly greater LDL-C reduction was achieved only at an Advicor dose of 2000/40 compared with lovastatin monotherapy. This was evident only after a requisite titration period of approximately 20 weeks due to the tolerability issues associated with Niaspan use. The LDL-lowering observed with Advicor at doses lower than 2000/40 did not provide any greater LDL reduction than with lovastatin monotherapy. Furthermore, no additional benefit to LDL-lowering was seen for Advicor over lovastatin monotherapy in male patients at any dose. In effect, Advicor at doses lower than 2000/40 provided no greater LDL-lowering advantage over lovastatin monotherapy and the greater LDL-lowering efficacy of Advicor 2000/40 was confined only to female patients. In aggregate, these data do not support the sponsor's proposed indication for Advicor as a first-line drug treatment for LDL-lowering.

The MA-06 efficacy results however, do support Advicor as a convenient product for patients who require treatment of elevated cholesterol and triglyceride levels and low high density lipoprotein cholesterol (HDL-C) levels that are not effectively treated with single agent therapy. Advicor was significantly better at LDL-lowering than Niaspan alone, and was significantly better at triglyceride (TG) lowering and HDL-raising than either Niaspan or lovastatin monotherapy. Although the MA-06 study results were not reproduced in a second controlled trial, there is sufficient clinical experience with the marketed products Niaspan and Mevacor to support a combination tablet of these two products.

The long-term, uncontrolled study MA-07 also found that Advicor produced dose-dependent decreases in LDL-C and TG, and increases in HDL-C. These results were durable over the 52 weeks of the study.

The safety findings in both the controlled and uncontrolled clinical studies suggest that Advicor is relatively safe for chronic administration. The majority of Adverse Events were not serious, and resolved when Advicor was discontinued or the dose was decreased. Advicor was poorly tolerated however, resulting in a high-drop out rate that continued into Year 2 of the extension study. This is a limitation for any drug intended for a chronic condition. Advicor's side-effect profile was similar to that of Niaspan and other niacin products. However, as Advicor is a combination product, it is recommended that the Advicor label contain the same precautions, warnings, and contraindications as are contained in both the Mevacor and Niaspan labels.

B. Summary of Clinical Findings

1. Overview of Clinical Program

Advicor is a combination tablet consisting of a niacin extended-release ——— lovastatin ——— The Sponsor plans to market Advicor as 500/20 (mg Niaspan/mg lovastatin), 750/20, and 1000/20 tablets.

The niacin extended-release component of Advicor is identical to another one of the Sponsor's marketed products, Niaspan. Niaspan has been shown in clinical trials to produce decreases in total cholesterol (TC), LDL-C, and TG, and increases in HDL-C. Niaspan is currently indicated:

- For the reduction of elevated TC, LDL-C, ApoB and TG levels, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and non-familial) and mixed dyslipidemias (type IIa and IIb)
- In patients with a history of myocardial infarction (MI) and hypercholesterolemia to reduce the risk of recurrent nonfatal MI
- In combination with a bile acid binding resin, to slow the progression or promote the regression of atherosclerotic disease, and for the reduction of elevated TC and LDL-C levels in patients with primary hypercholesterolemia (type IIa)
- For the treatment of adult patients with very high serum TG levels (types IV and V hyperlipidemia)

The lovastatin component is a generic version of Mevacor (Merck), a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor. Mevacor has been shown in clinical trials to significantly reduce TC and LDL-C, to modestly reduce TG, and to modestly increase HDL-C. Mevacor is currently indicated:

- For primary prevention of coronary heart disease (CHD) in patients with average to moderately elevated TC and LDL-C, and below average HDL-C
- To reduce the risk of MI, unstable angina, and coronary revascularization procedures, and to slow the progression of coronary atherosclerosis in patients with CHD
- In reducing TC and LDL-C in familial and non-familial forms of primary hypercholesterolemia and mixed dyslipidemia (type IIa and IIb)

The Advicor clinical program seeks to demonstrate the efficacy of combined niacin extended-release and lovastatin therapy on multiple lipid parameters, particularly LDL-C, and to demonstrate Advicor's safety and efficacy for chronic administration. The Sponsor's main goal for the NDA submission is that combination therapy with niacin extended-release and lovastatin (as Advicor) be approved for first-line treatment of hypercholesterolemia. To receive this indication, the Sponsor must demonstrate Advicor's advantage over single agent therapy by showing that Advicor is superior to lovastatin alone and Niaspan alone in the treatment of elevated LDL-C, and is safe for chronic administration based on Adverse Events (AEs), clinical examination, and laboratory assessments.

In addition, the Division will evaluate Advicor's TG-lowering and HDL-raising effect compared to the individual components of this product. In this setting, Advicor is considered a convenient second-line agent for patients who may require combination treatment for combined dyslipidemias or other lipid derangements. Advicor must therefore demonstrate better HDL-raising and TG-lowering than lovastatin alone, and better LDL-lowering than Niaspan alone.

The target patient population for the Advicor clinical program is adult men and women with hypercholesterolemia types IIa and IIb who are eligible for cholesterol lowering per NCEP guidelines.

The Sponsor submitted twelve clinical studies in support of NDA 21-249. Six of the twelve studies were pharmacokinetic studies, four studies were clinical safety and efficacy studies, and two were safety extension studies. Of the six pharmacokinetic studies, three studies were to define the pharmacokinetics and bioavailability of niacin and lovastatin from Advicor, and the remaining 3 were to compare the niacin ER —— manufactured at two different sites. All six studies were single-dose, open-label, crossover studies with oral administration, as follows:

1) Study 97/07: Open-label, randomized, single-dose, 2-way crossover comparison of the bioavailability of niacin and lovastatin from Advicor, Niaspan, and Mevacor [24 subjects].
2) Study CP-98-010418: Open-label, randomized, single-dose, 4-way crossover comparison of niacin and lovastatin from Advicor, Niaspan alone, Mevacor alone, and coadministration of Niaspan and Mevacor [40 subjects].
3) Study CP-98-010419: Open-label, randomized, single-dose, 3-way crossover comparison of the bioavailability of niacin and lovastatin from Advicor under fasting conditions, after a low-fat snack, and after a high-fat snack [27 subjects].
4) Study 97/04: Open-label, randomized, single-dose, 2-way crossover study to determine the bioequivalence of Niaspan 500 mg tablets manufactured at two different facilities [33 subjects].
5) Study 97/05: Open-label, randomized, single-dose, 2-way crossover study to determine the bioequivalence of Niaspan 1000 mg tablets manufactured at two different facilities [33 subjects].
6) Study CP-98-010420: Open-label, randomized, single-dose, 2-way crossover study to determine the bioequivalence of Advicor 750 mg —— tablets relative to Niaspan 750 mg tablets manufactured at two different facilities [33 subjects].

The above 6 studies have been reviewed in detail in the Biopharm review.

There were four clinical safety and efficacy studies, summarized as follows.

1) Study MA-98-010414 (MA-14) was a 20-week, double-blind, randomized, active-control, dose-response safety and efficacy study whose primary endpoint was to evaluate the mean percent change from baseline in LDL-C in patients treated with either Advicor (3 dosage groups), Niaspan, or lovastatin. Secondary efficacy

endpoints included mean percent change from baseline in HDL-C and TG, among other lipid parameters. Lipid levels were assessed every 4 weeks. MA-14 was conducted in 164 adult men and women (≥21 years of age) with Type IIa and IIb hyperlipidemia. There were 31-34 patients entered into each treatment group, and patients underwent a forced-dose titration schedule, as follows:

Table i: MA-14 Dose Titration Schedule

	Weeks				
Treatment	**1-4**	**5-8**	**9-12**	**13-16**	**17-20**
Niaspan (mg)	500	1000	1500	2000	2500
Advicor/10 (mg/mg)	500/10	1000/10	1500/10	2000/10	2500/10
Advicor/20 (mg/mg)	500/20	1000/20	1500/20	2000/20	2500/20
Advicor/40 (mg/mg)	500/40	1000/40	1500/40	2000/40	2500/40
Lovastatin (mg)	10	10	20	20	40

2) Study MA-98-010406 (MA-06) was a 28-week, double-blind, randomized, active-control, dose-response safety and efficacy study whose primary endpoint was to evaluate the mean percent change from baseline in LDL-C in patients treated with either Advicor (2 dosage groups), Niaspan, or lovastatin. Secondary efficacy endpoints included mean percent change from baseline in HDL-C and TG, among other lipid parameters. Lipid levels were assessed every 4 weeks. MA-06 was conducted in 236 adult men and women (≥18 years of age) with Type IIa and IIb hyperlipidemia. There were 57-61 patients entered into each treatment group, and patients underwent a forced-dose titration schedule, as follows:

Table ii: MA-06 Dose Titration Schedule

	Weeks						
Treatment	**1-4**	**5-8**	**9-12**	**13-16**	**17-20**	**21-24**	**25-28**
Advicor/20 (mg/mg)	500/20	750/20	1000/20	1000/20	1000/20	1000/20	1000/20
Advicor/40(mg/mg)	500/20	750/20	1000/20	1000/40	1500/40	2000/40	2000/40
Niaspan (mg)	500	750	1000	1000	1500	2000	2000
Lovastatin (mg)	20	20	20	40	40	40	40

3) Study MA-98-040107 (MA-07) was a 52-week, open-label, uncontrolled study whose primary objective was to evaluate the long-term safety and efficacy of Advicor. The primary endpoint was the mean percent change from baseline in LDL-C, and secondary efficacy endpoints included mean percent change from baseline in HDL-C and TG, among other lipid parameters. Lipid levels were assessed every 4 weeks until Week 16, then every 12 weeks until study conclusion. MA-07 was conducted in 814 adult men and women (≥21 years of age) with Type IIa and IIb hyperlipidemia. All patients received Advicor and underwent a forced-dose titration schedule, as follows:

Table iii: MA-07 Dose Titration Schedule

	Week					
	0-4	5-8	9-12	13-16	17-28	29-52
Advicor dose (mg/mg)	500/10	1000/20	1500/30	2000/40	2000/40	2000/40

The investigator could decrease the dose of study medication for patient tolerability or safety after the patient had completed the dose-escalation phase of the study.

4) Study — was ——————————————————————————————— This study did not involve the administration of Advicor, and did not support the Sponsor's proposed labeling for Advicor. Study — was therefore not reviewed in detail and was considered only as additional safety information for Niaspan.

The two safety extension studies were submitted to the NDA as an 8-month safety update. The two studies are summarized as follows.

1) Study MA-98-010407 Extension Study was a 48-Week extension to the MA-07 study. The study design was the same as for MA-07, and 300 patients were rolled-over (enrolled) in the extension study after successfully completing the initial 52 weeks of MA-07. The primary objective was to evaluate the long-term safety and efficacy of Advicor, and the primary endpoint was the mean percent change from baseline in LDL-C. Secondary efficacy endpoints included mean percent change from baseline in HDL-C and TG, among other lipid parameters. Lipid levels were assessed every 12 weeks until study conclusion. All patients were continued on the same dose of open-label Advicor as they were receiving in the 52-week study, and the investigator could decrease the dose of study medication for patient tolerability or safety.

2) Study MA-98-010409 (MA-09) was a 48-week extension study to the MA-14 and MA-06 studies. One hundred-six (106) patients who had successfully completed MA-14 or MA-06 were enrolled in MA-09. The primary objective was to evaluate the long-term safety and efficacy of Advicor, and the primary endpoint was the mean percent change from baseline in LDL-C. Secondary efficacy endpoints included mean percent change from baseline in HDL-C and TG, among other lipid parameters. Lipid levels were assessed every 4 weeks until Week 17, then every 12 weeks. All patients received Advicor starting at a dose of 500/20 once daily, and were forced dose-titrated as follows:

Table iv: MA-09 Dose Titration Schedule

	Week				
	0-4	5-8	9-12	13-16	17-48
Advicor dose (mg/mg)	500/20	1000/40	1500/40	2000/40	2000/40

The investigator could decrease the dose of study medication for patient tolerability or safety.

2. Efficacy

The efficacy conclusions for the two double-blind controlled studies MA-14 and MA-06 are summarized as follows.

The review of MA-14 raised several problems with both the study design and the study results. There was a poor LDL-lowering response in the lovastatin group compared to historical data and to internal controls, and as the comparative efficacy of Advicor vs lovastatin for LDL-lowering was a primary endpoint, the efficacy results were uninterpretable. More importantly however, the study design did not provide for valid comparisons between the to-be-marketed Advicor doses and lovastatin. The MA-14 study was, therefore, not supportive of the proposed labeling. The efficacy results for MA-14 are inconclusive and will not be considered in the approval process of Advicor.

The review of MA-06 efficacy data shows that:

1) Advicor 2000/40 achieved a significantly greater LDL-C reduction than lovastatin 40 mg only after 24 weeks of dose-titration of Advicor.
2) On subgroup analysis, a significantly better result for LDL-lowering was seen only in female patients. There was no difference in LDL-lowering seen for male patients with Advicor compared to lovastatin at any dose and for any time point.
3) Advicor achieved significantly greater LDL-lowering than Niaspan at all dosage comparisons.
4) For the secondary endpoints, Advicor was significantly better than Niaspan alone and lovastatin alone for HDL-raising at all doses. Advicor was also better than lovastatin for TG-lowering at doses of 1000/20 or higher, and was better than Niaspan for TG-lowering at doses of 750/20 or higher.

These findings do not support the use of Advicor as a first-line treatment for LDL-lowering. Advicor had no LDL-lowering benefit over lovastatin monotherapy at doses lower than 2000/40. Furthermore, Advicor was found to be beneficial for LDL-lowering only in female patients. Male patients do not receive any additional LDL-lowering with Advicor over lovastatin alone. However, as Advicor was found to be significantly better than Niaspan alone for LDL-lowering, and was better than lovastatin alone for HDL-raising and TG-lowering (at doses 1000/20 and higher), Advicor could be considered for use as a convenient product for patients who require combination therapy with Niaspan and lovastatin to treat multiple dyslipidemias.

The efficacy results for MA-07 show that Advicor produced dose-dependent LDL-C and TG-lowering, and HDL-C raising that were durable throughout the 52 weeks of the study. There were greater responses seen for LDL-C and TG-lowering, and HDL-raising in female patients compared to male patients, and geriatric patients appeared to have at least as great a response to the lipid-altering effects of Advicor as non-geriatric patients.

There were no efficacy data submitted for the MA-07 extension study and the MA-09 study .

3. Safety

The safety findings in the two double-blind studies, MA-14 and MA-06, were similar. Overall, Advicor was not well tolerated, and more patients in the niacin-exposed groups reported any AEs during study drug treatment than patients in the lovastatin group. This resulted in more niacin-exposed patients discontinuing study drug treatment prior to study completion. Flushing and rash were the most commonly reported reasons for discontinuation in both studies, and occurred more frequently in the niacin-exposed groups. Female patients were somewhat more likely to be discontinued from the study than male patients, most commonly due to AEs, especially flushing. Geriatric patients were more likely than non-geriatric patients to discontinue in the MA-14 study, but there was no difference between the groups for discontinuations in the MA-06 study. Clinically significant treatment emergent laboratory abnormalities were uncommon. No patient discontinued for a laboratory abnormality in MA-14, and 2 patients discontinued for a laboratory abnormality in MA-06, both of which were fasting blood sugar (FBS) elevations. Mild elevations in AST, ALT, FBS, and CPK, and mild to moderate decreases in phosphorous were common in both studies. FBS increases were the most common treatment-emergent laboratory abnormality (TELA), occurring in >50% of patients in MA-14 and MA-06, and were more common in the niacin-exposed groups in MA-14 only.

The most common AEs occurring in the MA-06 are as follows (similar results were obtained in MA-14):

Table v: MA-06 Incidence of Most Common Adverse Events by Body System

			Treatment			
		All	**Advicor/20**	**Advicor/40**	**Niaspan**	**Lovastatin**
ITT Patients, n =		236	57	57	61	61
Body System		n (%)	n (%)	n (%)	n (%)	n (%)
Body as a whole	**All**	**126 (53)**	**35 (61)**	**32 (56)**	**33 (54)**	**26 (43)**
	Infection	52 (22)	17 (30)	13 (23)	10 (16)	12 (20)
	Headache	28 (12)	11 (19)	5 (9)	9 (15)	3 (5)
	Pain	23 (10)	4 (7)	8 (14)	5 (8)	6 (10)
	Flu syndrome	15 (6)	3 (5)	5 (9)	3 (5)	4 (7)
	Pain, back	15 (6)	6 (11)	0	4 (7)	5 (8)
Cardiovascular	**All**	**156 (66)**	**49 (86)**	**48 (84)**	**43 (71)**	**16 (26)**
	Flushing	148 (63)	47 (83)	47 (83)	42 (69)	12 (20)
Digestive	**All**	**51 (22)**	**14 (25)**	**14 (25)**	**13 (21)**	**10 (16)**
	Nausea	13 (6)	3 (5)	6 (11)	4 (7)	0
	Diarrhea	11 (5)	3 (5)	4 (7)	2 (3)	2 (3)
Skin and Appendages	**All**	**41 (17)**	**9 (16)**	**12 (21)**	**13 (21)**	**7 (12)**
	Rash	16 (7)	2 (4)	3 (5)	9 (15)	2 (3)
	Pruritus	12 (5)	2 (4)	6 (11)	3 (5)	1 (2)

The safety results for the 3 uncontrolled, long-term studies were similar to the two double-blind studies. The types and frequencies of AEs were similar, and flushing

continued to be the most commonly reported AE. The most commonly reported reasons for discontinuation due to AEs in the MA-07 study were flushing (10%), pruritus (4%), and rash (2%). Discontinuations for laboratory abnormalities resulted from elevations in ALT, AST, FBS, CPK, and bilirubin, and from decreases in platelet counts. Mild abnormalities were commonly seen in ALT, AST, FBS, phosphorous, and CPK. Mild FBS elevations were the most commonly observed laboratory abnormalities, and occurred in 64% of patients overall. Serious AEs occurred in 6% of study patients, most commonly in the Cardiovascular and Gastrointestinal systems.

The safety findings in both the controlled and uncontrolled clinical studies suggest that Advicor is relatively safe for chronic administration. The majority of AEs were not serious, and resolved when Advicor was discontinued or the dose was decreased. Advicor was poorly tolerated however, resulting in a high-drop out rate (approximately 33% in most of the studies), that even continued into Year 2 of the MA-07 extension study. This suggests that tolerance to the side-effects of Advicor, particularly flushing, does not substantially improve with long-term treatment as has previously been suggested. This will likely limit Advicor's clinical utility.

Advicor's side-effect profile was found to resemble that of Niaspan and other niacin products. As Niaspan and Mevacor are both widely prescribed, marketed products, there is considerable clinical experience with both of these drugs and their safety profiles are well established. As Advicor is a combination product, it is recommended that the Advicor label contain the same precautions, warnings, and contraindications as are contained in both the Mevacor and Niaspan labels.

4. Dosing

Advicor is a fixed-dose combination product and is not indicated for initial therapy as a lipid-altering agent. Current guidelines for treatment with cholesterol-lowering agents recommend that initial therapy begin with a single agent, and that combination therapy be reserved for patients with inadequate responses to single-agent treatment in whom the lipid-lowering benefits outweigh the potential risks of combination therapy.

The clinical efficacy data for Advicor support an indication for the treatment of primary hypercholesterolemia and mixed dyslipidemia in:

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

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Dosing guidelines for Advicor should include:

- For patients not already receiving Niaspan, the usual starting dose is 500 mg qhs, and Niaspan is then titrated up by 500 mg every 4 weeks, to a maximum dose of 2000 mg a day.

- For patients not already receiving lovastatin, the usual starting dose is 20 mg a day, with dose adjustments made at intervals of 4 weeks or more.
- Patients receiving lovastatin who may benefit from the addition of niacin therapy should receive dosage titration with Niaspan. Once a stable niacin dose has been reached, patients can be switched to an Advicor dose that contains the equivalent Niaspan component.
- The Advicor clinical program did not study lovastatin in combination with Niaspan at doses of lovastatin higher than 40 mg, and current clinical data do not support the use of Advicor at doses greater than 2000/40.

5. Special Populations

There were greater responses seen for LDL-C and TG-lowering, and HDL-raising in female patients compared to male patients, and geriatric patients appeared to have at least as great a response to the lipid-altering effects of Advicor as non-geriatric patients. There were too few non-Caucasian patients in any of the studies to evaluate by Race. Advicor is contraindicated in women who are or may become pregnant and in lactating mothers. Advicor may cause fetal harm when administered to pregnant women. At this time, as hypercholesterolemia as a risk factor for CHD is primarily a concern for adult patients, the Sponsor requested and was granted a pediatric waiver. No pediatric studies were performed and the Division is not aware of any studies that are currently planned for pediatric patients.

II. Introduction

A. Historical Background

Coronary heart disease (CHD) is the leading cause of death in both men and women in the United States (US), and hypercholesterolemia has been well established as a major risk factor for CHD. Large epidemiologic studies have shown that the relationship between serum cholesterol and CHD is continuous and graded over the entire range of serum cholesterol values, and that the risk of CHD rises steadily with increasing serum cholesterol[1, 2]. Large clinical endpoint trials aimed at reducing total cholesterol (TC) or low density lipoprotein cholesterol (LDL-C) have shown a reduction in the risk of CHD death and acute, major cardiovascular (CV) events with cholesterol-lowering therapy[3, 4]. These trials have demonstrated risk reductions in patients with established CHD (primary prevention)[5, 6], and without CHD (secondary prevention)[7, 8, 9] across a broad range of baseline cholesterol levels. While some of the strongest evidence for risk reduction in CHD with cholesterol-lowering therapy has been demonstrated in trials using HMG-CoA reductase inhibitors (statins), risk reductions have also been shown with other cholesterol-lowering interventions, such as diet, fibrates, and bile-acid sequestrants.

Although LDL-C and TC levels have been the primary focus for lipid-lowering therapy, other components of the lipid profile have also been recognized as atherogenic. For example, low serum high density lipoprotein cholesterol (HDL-C) and triglyceride-rich lipoproteins have been established as consistent and important risk factors for CHD in large epidemiologic and clinical outcomes trials[10]. A recent study, The Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) study published in 1999, demonstrated a risk reduction in CHD morbidity and mortality in men with CHD whose primary lipid abnormality was a low HDL-C[11]. The VA-HIT study showed that intervention with gemfibrozil reduced the rate of CV events by raising HDL-C and lowering triglyceride (TG) levels without lowering LDL-C. This result is similar to the risk reductions in CV events previously shown in studies aimed at LDL-lowering.

The majority of clinical trials evidence confirms that CHD morbidity and mortality can be reduced by the treatment of risk factors such as dyslipidemia, and that lipid-altering therapy can reduce this risk by about 25-35%. In accordance with recent clinical trials evidence, the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults presented updated recommendations for cholesterol management in May, 2001[12]. The panel continued to identify LDL-C as the primary target of cholesterol-lowering therapy and to recommend the increased emphasis on CHD risk status as a guide to the type and intensity of cholesterol-lowering therapy. Adult Treatment Panel III (ATP III) guidelines recommend LDL-lowering drug therapy be initiated with a single agent. Intensification of drug therapy, either by increasing the dose of the drug or by combining a statin with another agent, should be undertaken only if the LDL goal has not been achieved. The use of other lipid-modifying agents other than statins (e.g., niacin or a fibrate), or combination therapies, are to be considered in patients whose LDL-C is at goal, but who have elevated TG (>200 mg/dL); however, it is

emphasized that non-HDL-C is the secondary target for risk reduction, after the primary target of LDL-C. Current drug treatment guidelines recommend LDL-C treatment goals based on CHD risk as follows

Table 1: NCEP Guidelines for Cholesterol Reduction

Patient Category	LDL-C goal (mg/dL)	LDL-C Treatment Initiation Level (mg/dL)
Without CHD and with fewer than 2 risk factors (10-year risk of major coronary events <10%)	<160	≥190 (160-189: LDL-lowering optional)
Without CHD and with 2 or more risk factors (10-year risk ≤20%)	<130	10-year risk 10-20%: ≥130 10-year risk <10%: ≥160
With CHD or CHD risk equivalents, e.g., diabetes (10-year risk >20%)	≤100	≥130 (100-129: drug optional)

B. Rationale for the Advicor Clinical Program

The Sponsor has proposed the intended use of Advicor

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(Italics mine. From: Kos Pharmaceuticals, NDA #21-249, NDA Summary, Volume 1, page 42).

The Sponsor's rationale for the development of Advicor as a first-line agent is quoted from the NDA summary as follows: *"Effective treatment for the majority of patients at risk, especially in light of the increase in prevalence in CHD expected in the next several decades, will likely then require broad-spectrum lipid control, not just LDL-C reduction. ... there is evidence from smaller studies that combination therapy with its broad spectrum effects on the lipid profile will achieve greater reductions in coronary incidence compared to monotherapy."* (Italics mine. From: Kos Pharmaceuticals, NDA #21-249, NDA Summary, Volume 1, page 40)

The Sponsor states that combination therapy with lipid-altering agents that target multiple components of the lipid profile are expected to reduce the relative risk of CV events to a greater extent than treatment with single agents. Small studies using combination therapy have shown improvements in multiple components of the lipid profile[13], and in angiographic endpoints[14, 15], and in at least one study, the incidence of clinical CV endpoints has been reduced[16].

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Additionally, as the trials performed in the Advicor clinical program were designed to demonstrate the lipid-altering effects of Advicor

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The Advicor program seeks to demonstrate the efficacy of combined niacin extended-release and lovastatin therapy on multiple lipid parameters, particularly LDL-C. The

Sponsor intends to demonstrate that combination treatment with Advicor will be superior to lovastatin and Niaspan monotherapy in the treatment of elevated LDL-C and TG, and low HDL-C. In keeping with ATP III guidelines (see Historical Background), the Division will also be evaluating Advicor as a second-line agent for patients who may require combination treatment for other lipid derangements, such as elevated TG and low HDL-C. As a second-line, convenient product, Advicor must demonstrate better HDL-raising and TG-lowering than lovastatin alone, and better LDL-lowering than Niaspan alone.

Finally, as dyslipidemias are chronic conditions that will, in most patients, require long-term treatment with lipid-altering drugs, any drug indicated for use as a lipid-altering agent (either for single use or for use in combination therapy) would need to demonstrate long-term safety as well as efficacy. This is especially important for a combination lipid-altering therapy that has been shown to be associated with an increased risk of serious side-effects, most notably myopathy and rhabdomyolysis[17]. It is important to note, however, that the number of patients exposed to Advicor in this NDA is insufficient to address the risk of myopathy and rhabdomyolysis with combination therapy.

C. Clinical Experience With Mevacor (lovastatin) and Niacin

1. Mevacor

Mevacor has been approved by the Agency as a cholesterol-lowering agent, and is indicated for the treatment of dyslipidemia in patients at risk for atherosclerotic vascular disease[18]. Mevacor is approved for use as primary prevention of CHD in patients with average to moderately elevated TC and LDL-C, and below average HDL-C. Mevacor is indicated to reduce the risk of myocardial infarction (MI), unstable angina, and coronary revascularization procedures, and it has been shown to slow the progression of coronary atherosclerosis in patients with CHD. Mevacor also has been shown to be effective in reducing TC and LDL-C in familial and non-familial forms of primary hypercholesterolemia and mixed dyslipidemia (type IIa and IIb).

a) Efficacy

In a multi-center, double-blind, placebo-controlled clinical study in patients with primary hypercholesterolemia, Mevacor in doses ranging from 10-40 mg once a day was compared to placebo. Mevacor significantly reduced TC and LDL-C, modestly reduced TG, and modestly increased HDL-C after 6 weeks of treatment. Results from this study, per the Mevacor package insert, are summarized in the following table

Table 2: Mean % Change From Baseline in Lipids, Mevacor Package Insert

Treatment	n =	TC	LDL-C	HDL-C	TG
Placebo	33	-2	-1	-1	+9
Mevacor, dose					
10 mg qD	33	-16	-21	+5	-10
20 mg qD	33	-19	-27	+6	-9
10 mg BID	32	-19	-28	+8	-7
40 mg qD	33	-22	-31	+5	-8
20 mg BID	36	-24	-32	+2	-6

Mevacor was evaluated for long-term safety and efficacy in the Expanded Clinical Evaluation of Lovastatin (EXCEL) study[19]. EXCEL was a large (n = 8,245), multi-center, double-blind, randomized, placebo-controlled, clinical trial, which compared Mevacor in doses from 10-80 mg a day to placebo. Mevacor showed statistically significant decreases in TC and LDL-C, modest decreases in TG, and modest increases in HDL-C. These changes were sustained throughout 48 weeks of treatment, and similar results were obtained in the 2-year extension arm of the study[20]. Results for the EXCEL study (after 48 weeks of treatment) are summarized in the following table

Table 3: Mean % Change From Baseline in Lipids, EXCEL study

Dose	n	TC	LDL-C	HDL-C	TG
Placebo	1663	+0.7	+0.4	+2	+4
Mevacor 20 mg	1642	-17	-24	+6.6	-10
Mevacor 40 mg	1645	-22	-30	+7.2	-14
Mevacor 80 mg (40 mg BID)	1649	-29	-40	+9.5	-19

The Sponsor is proposing Advicor as a first-line treatment for the [redacted] and has proposed using data from Mevacor clinical endpoint trials as justification for this indication. Although not directly relevant to this NDA as the Sponsor has not submitted any clinical endpoint data to the application, the Mevacor clinical endpoint trials will be briefly reviewed here.

Mevacor has been evaluated in a large clinical endpoint study, the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), for the primary prevention of major coronary events[6]. AFCAPS/TexCAPS was a multi-center, randomized, placebo-controlled trial in 6,605 patients with elevated TC and LDL-C, below average HDL-C, and no history of CV disease. Treatment with Mevacor compared to placebo resulted in statistically significant mean decreases in TC, LDL-C and TG, and increases in HDL-C, and was shown to decrease the rate of major coronary events compared to placebo by 37% over the course of 5.2 years. The relative risk of the secondary endpoint (unstable angina, MI, and cardiovascular revascularization procedures) was also reduced by 33%.

Mevacor has also been evaluated in smaller clinical angiographic endpoint trials for the treatment of atherosclerosis. Three of these studies are: the Canadian Coronary

Atherosclerosis Intervention Trial (CCAIT); the Monitored Atherosclerosis Regression Study (MARS); and the Asymptomatic Carotid Artery Progression Study (ACAPS). Two of these studies (CCAIT and MARS) investigated the effects of lovastatin on coronary atherosclerosis, and the other (ACAPS) investigated lovastatin's effects on carotid atherosclerosis.

CCAIT was a randomized, double-blind, placebo-controlled study in 331 patients with hypercholesterolemia and diffuse coronary atherosclerosis, who were treated with either placebo or lovastatin 20-80 mg daily[21]. Coronary arteriograms were assessed at baseline and after 2 years of treatment, and were assessed by visual estimation and computerized quantitative measurement. Lovastatin was shown to significantly slow the progression of lesions [measured by the mean change per-patient in minimum lumen diameter (primary endpoint), and percent diameter stenosis], to significantly decrease the proportion of patients categorized with disease progression (lovastatin 33% vs placebo 50%), and to significantly decrease the proportion of patients with new lesions (lovastatin 16% vs placebo 32%). The clinical relevance of these findings is uncertain as the difference in coronary change of score between the treatments was small (0.04 mm). The findings were not associated with a reduction in coronary events during the trial.

MARS was a randomized, double-blind, placebo-controlled study in 270 patients with hypercholesterolemia and angiographically defined coronary artery disease (CAD)[22]. Patients were treated with either placebo or lovastatin 80 mg a day for 2 years. Coronary angiograms were assessed at baseline and after 2 years of treatment. There was no statistically significant difference between the groups in the primary end point (change in percent diameter stenosis). Treatment with lovastatin was found to slow the overall rate of progression (by global change score) [29% of lovastatin patients progressed vs 41% of placebo patients] and increased the overall rate of regression [23% of lovastatin patients vs 11% of placebo patients]. No statistical differences were observed between groups in the proportion of patients with clinical coronary events.

ACAPS was a randomized, double-blind, placebo-controlled study in 919 patients with moderately elevated LDL-C, early carotid atherosclerosis and no history of CHD[23]. Patients were randomized to four combination therapy groups: lovastatin/warfarin, lovastatin/warfarin placebo, lovastatin placebo/warfarin, or lovastatin placebo/warfarin placebo. Patients were assessed by carotid B-mode ultrasound at baseline and after 3 years of treatment. There was a statistically significant regression in carotid lesions [as measured by the maximum intimal-medial thickness (IMT)] in the lovastatin alone vs placebo alone groups (primary endpoint), and a reduction in the risk of major CV events (5 lovastatin patients experienced events vs 14 placebo patients), and all-cause mortality (1 lovastatin patient died vs 5 placebo patients).

All of the above studies involved lipid-altering treatment with lovastatin monotherapy (warfarin in the ACAPS study was not used as a lipid-altering agent). These results cannot be interpreted as also applying to niacin and lovastatin in combination, as it is not known if similar results would be obtained with combination therapy.

b) Safety

In clinical studies, Mevacor has been found to be generally well tolerated. In the EXCEL study, patients taking Mevacor experienced clinical adverse events of similar types and frequencies to those of placebo patients. In patients up to 48 weeks of treatment, 4.6% of patients treated were discontinued due to clinical or laboratory adverse events (AEs) [rated by the Investigator as at least possibly related to study medication] vs 2.5% of placebo patients. Mevacor and other HMG-CoA reductase inhibitors occasionally cause myopathy, and rarely, rhabdomyolysis. In EXCEL, there was one case of myopathy among 4,933 patients randomized to lovastatin 20-40 mg a day, and 4 cases of myopathy among 1649 patients randomized to 80 mg a day. The risk of myopathy is increased by concomitant therapy with certain drugs, including gemfibrozil and other fibrates, niacin, and CYP3A4 inhibitors, such as cyclosporine, azole antifungals, macrolide antibiotics, HIV protease inhibitors, nefazodone, and large quantities of grapefruit juice. Persistent increases in serum transaminases occurred in up to 1.9% of adult patients who received lovastatin for at least one year in clinical trials. The incidence rates by dose are summarized in the following table:

Table 4: Mevacor, Incidence of Persistent Serum Transaminase Elevations, EXCEL Study

Treatment	Incidence of Persistent Serum Transaminase Increases
Placebo	0.1%
Mevacor 20 mg a day	0.1%
Mevacor 40 mg a day	0.9%
Mevacor 80 mg a day	1.5%

In AFCAPS/TexCAPS, the number of participants with consecutive elevations of ALT or AST was not significantly different between Mevacor and placebo over a median of 5.1 years of follow-up [Mevacor 0.6% vs placebo 0.3%]. Elevated transaminases resulted in the discontinuation of 6 patients (0.2%) from the Mevacor group (n=3,304) vs 4 patients (0.1%) from the placebo group (n=3,301). In post-marketing experience, symptomatic liver disease has been reported rarely at all doses.

2. Niacin

Niacin immediate-release formulations have been in clinical use for decades as a treatment to reduce elevated TC and TG levels, and for the treatment of types II, III, IV, and V hyperlipoproteinemia[24]. Its clinical use has been limited however, as niacin immediate-release has been poorly tolerated. Sustained-release formulations of niacin were developed to try to reduce the incidence of side-effects and improve tolerability;

[ ] Niaspan (niacin extended-release) was approved by the Agency in 1997, and has a safety profile similar to the immediate-release formulations.

Niaspan is indicated for the reduction of elevated TC, LDL-C, ApoB and TG levels, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and non-familial) and mixed dyslipidemias (type IIa and IIb)[25]. Niaspan is indicated in patients with a history of MI and hypercholesterolemia to reduce the risk of recurrent nonfatal MI. In combination with a bile acid binding resin, Niaspan is indicated to slow the progression or promote the regression of atherosclerotic disease, and for the reduction of elevated TC and LDL-C levels in patients with primary hypercholesterolemia (type IIa). Niaspan is also indicated for the treatment of adult patients with very high serum TG levels (types IV and V hyperlipidemia).

a) Efficacy

In two double-blind, placebo-controlled clinical studies in patients with primary hypercholesterolemia and mixed dyslipidemia, Niaspan has been shown to produce dose-dependent decreases in LDL-C, TG, TC, and Lp(a), and increases in HDL-C. Women had a greater response than men at each dose level. The mean % changes in lipids from baseline after 16 weeks of treatment, including dose titration, are summarized as follows

Table 5: Mean % Change From Baseline in Lipids, Niaspan Package Insert

Dose	n	TC	LDL-C	HDL-C	TG	Lp(a)
Study 1						
Placebo	40	0	-1	+4	-13	-15
Niaspan 1000 mg	41	-3	-5	+18	-21	-13
Niaspan 2000 mg	41	-10	-14	+22	-28	-27
Study 2						
Placebo	73	+2	+1	+2	+12	+2
Niaspan 1500 mg	76	-8	-12	+20	-13	-15

In another double-blind, forced dose-escalation study, Niaspan was initiated at 500 mg a day, and increased by 500 mg monthly, up to a dose of 2000 mg a day. Mean % changes in lipid levels at each dose in the same patients is as follows

Table 6: Mean % Change From Baseline in Lipids, Niaspan Package Insert Forced Dose-Titration Study

Treatment	n	TC	LDL-C	HDL-C	TG	Lp(a)
Placebo	44	-2	-1	+5	-6	-5
Niaspan dose	87					
500 mg		-2	-3	+10	-5	-3
1000 mg		-5	-9	+15	-11	-12
1500 mg		-11	-14	+22	-28	-20
2000 mg		-12	-17	+26	-35	-24

As previously stated, the Sponsor is proposing Advicor as a first-line treatment for — ——————— and has proposed using data from niacin clinical endpoint trials as justification for this indication. Niaspan monotherapy has not been evaluated in any clinical endpoint trials, however niacin immediate-release has been evaluated in a large clinical endpoint trial, the Coronary Drug Project, which will be briefly reviewed here.

The Coronary Drug Project (CDP), was a six-treatment arm study begun in 1966, which enrolled over 8,000 men ages 30-64 years, with a previous history of MI[26]. The primary objective of the CDP was to evaluate the efficacy and safety of several lipid-influencing drugs in the long-term treatment of CHD, and the primary endpoint was mortality. Other endpoints included cause-specific mortality, particularly coronary mortality, sudden death, and nonfatal cardiovascular events. Niacin produced sustained mean reductions in TC and TG levels of about 10% and 26% respectively. At the five-year follow up (study conclusion), there was no statistically significant benefit to niacin regarding total mortality and cause-specific mortality. However, there was a statistically significantly lower incidence of definite, nonfatal MI in the niacin group vs the placebo group. Patients were again followed-up at 15 years, 9 years after study termination, and the niacin group was found to have an 11% lower mortality than in the placebo group[27]. The late benefit was felt to be secondary to the early favorable decrease in non-fatal MI, with a resultant lower mortality in subsequent years.

These results cannot be interpreted as also applying to niacin and lovastatin in combination as it is not known if the results from this study would also be obtained with combination therapy.

b) Safety

Most adverse events associated with niacin use are dose-related and subside with the discontinuation or reduction in the dose of the drug. To reduce the incidence and severity of AEs, the dose of niacin must be titrated up over a number of months. In some patients, tolerance to AEs may develop within 2-6 weeks after initiation of niacin. The most commonly occurring side-effects associated with niacin use include (but are not limited to):

Cardiovascular:	flushing (in up to 88% of patients), dizziness, tachycardia, palpitations and syncope
Gastrointestinal:	nausea, vomiting, diarrhea and dyspepsia
Skin:	pruritus and rash

Laboratory abnormalities frequently associated with niacin use include (but are not limited to):

Elevations in:	AST and ALT, CPK, PT, uric acid, and dose-related increases in serum glucose.
Decreases in:	platelet count, white blood cell count (WBC), absolute neutrophil count (ANC), and phosphorous

In clinical trials with Niaspan, elevations in AST and ALT >3 X the upper limit of normal (ULN) were reported in about 1% of patients, and discontinuations due to AST and ALT elevations >2 X ULN were <1%. Elevations appear to be dose related, but are not related to treatment duration. Myopathy has been reported with the use of niacin, and rhabdomyolysis has been associated with concomitant administration of niacin and statins.

Safety results in the CDP were consistent with other reports on long-term niacin use. Discontinuations in the niacin group occurred in 10.7% of patients vs 7.4% in the clofibrate group, and 8.0% in the placebo group. The most common complaints were dermatological problems of flushing, itching, and rash. Other complaints included gastrointestinal and urinary tract symptoms, elevations in serum uric acid levels, a greater incidence of gouty arthritis, elevated SGOT (AST), CPK, alkaline phosphatase, and plasma glucose levels, and lower levels of serum total bilirubin, plasma BUN, urine protein, serum potassium, WBC and ANC. There was also a statistically significantly higher incidence of atrial fibrillation and other arrhythmias. The CLAS study noted a statistically significant higher prevalence in the niacin-colestipol group of skin related (flushing, warmth, itching, rash, tingling or dry skin) or gastrointestinal (constipation, nausea, stomach discomfort, heartburn, diffuse abdominal pain, vomiting and sore throat) symptoms. There was also a significantly higher prevalence of laboratory abnormalities, including increases in alkaline phosphatase, AST, and uric acid, and decreases in thyroxin and carotene.

3. Combination Studies

The majority of reports in the literature on the use of combination therapy with niacin and lovastatin (or niacin and another statin) are small case-series reports. These case-series reports focus predominantly on the effects of combination therapy on the lipid profile and on the short-term safety of the combination. These case-series also usually involve patients with combined dyslipidemia or severe hyperlipidemias not well controlled with single agents. These studies do not support the current NDA and will not be considered further.

One study that investigated combination therapy in a controlled design was the Harvard Atherosclerosis Reversibility Project (HARP) Study. HARP was a randomized, placebo-controlled, 2.5 year study in 91 normolipidemic patients with CHD which investigated combination therapy with pravastatin, niacin, cholestyramine, and gemfibrozil[13]. HARP compared patients receiving usual care with patients receiving stepped-care drug therapy titrated to LDL-C treatment goals. Stepped care consisted of an HMG-CoA reductase inhibitor (pravastatin) as initial therapy followed by the addition of slow release niacin, cholestyramine, or gemfibrozil as indicated. The study demonstrated that most patients required combination therapy to achieve treatment goals, and that the combination of pravastatin and niacin produced substantial improvements in LDL-C and HDL-C. Of note, 16% of patients who received niacin discontinued therapy after a mean of 40 weeks, compared to 2% of patients receiving monotherapy (pravastatin). There were no clinical endpoints in this study. While this study demonstrates the effects of a statin and niacin on the lipid profile, the dosing and titration schedules were vastly different from the Advicor controlled studies submitted to the NDA. HARP also involved the use of pravastatin, not lovastatin. For these reasons, HARP will not be considered further and will not be included in the Advicor labeling.

Two other studies in the literature using combination therapy that will be briefly discussed are the Familial Atherosclerosis Treatment Study (FATS) and the Cholesterol-Lowering Atherosclerosis Study (CLAS).

FATS was a six-year randomized, double-blind, placebo-controlled study in 146 men with elevated apo B levels and a family history of CAD[14]. Patients had evidence of coronary atherosclerosis on a baseline arteriogram. Patients were randomized to treatment with colestipol+lovastatin, colestipol+niacin, or placebo. Combination therapy with either niacin or lovastatin with colestipol resulted in decreased progression of coronary atherosclerosis, an increased frequency of coronary atherosclerotic regression, and a reduced incidence of CV events (death, MI, or the need for revascularization procedures). These findings are not directly relevant to Advicor as niacin and lovastatin were not administered in combination, and it is unknown if the findings for colestipol administered with either niacin or lovastatin would be similar to niacin and lovastatin in combination.

Patients completing FATS were offered to continue indefinitely on triple therapy with niacin, lovastatin and colestipol after completion of the original study. Seventy-five (75) patients continued with a subsequent median follow-up of eight years[16]. The patients who declined further participation were returned to usual care (n = 101) and had a median follow-up of 10 years. Clinical event rates in the triple therapy group were significantly reduced compared to the usual care group (5.3% vs 18.8% respectively), and the event curves diverged steadily over 8-10 years. Triple therapy was not part of the original treatment plan, was added as an extension after the original study was completed, and was an open-label, uncontrolled design. It is not known if the treatment groups were balanced, and if the results of triple therapy are applicable to the niacin/lovastatin combination. Therefore, the results of the FATS extension study will not be included in the Advicor labeling.

CLAS was a randomized, selectively-blinded, placebo-controlled study that evaluated the effect of LDL-lowering and HDL-raising on atherosclerotic lesions in the coronary, femoral and carotid arteries[15]. One hundred sixty-two (162) patients with previous coronary bypass surgery were treated with either placebo or niacin + colestipol for 2 years, and combined coronary, femoral, and carotid angiograms were obtained at baseline and after two years of therapy. The average global change score (primary endpoint) was significantly smaller (less disease progression) in the niacin-colestipol group than in the placebo group. The niacin-colestipol group had a significant reduction in the average number of lesions that progressed and in the percentage of subjects with new lesions vs placebo. There were no differences between the groups in major medical events (including CV events). The angiographic findings were confirmed 2 years later in the CLAS-II study, when 103 of the original CLAS patients were followed-up after 4 years of treatment[28]. The combination of colestipol and niacin is not directly relevant to the Advicor NDA as it is unknown if similar results would be obtained with niacin and lovastatin in combination. This study will not be considered further, and the findings do not support the proposed Advicor labeling.

D. The Advicor Clinical Program

1. Clinical Studies

The sponsor has submitted twelve clinical studies in support of NDA 21-249. Six of the twelve studies were pharmacokinetic studies, four studies were clinical safety and efficacy studies, and two were safety extension studies. Of the six pharmacokinetic studies, three studies were to define the pharmacokinetics and bioavailability of niacin and lovastatin from Advicor, and the other 3 pharmacokinetic studies were to compare the niacin ER manufactured at different sites. All six studies were single-dose, open-label, crossover design studies with oral administration. The six pharmacokinetic studies are summarized in the following table

Table 7: Advicor Pharmacokinetic Studies

Protocol Number	Study Design
97/07	Open-label, randomized, single-dose, 2-way crossover comparison of the bioavailability of niacin and lovastatin from Advicor, Niaspan and Mevacor
CP-98-010418	Open-label, randomized, single-dose, 4-way crossover comparison of niacin and lovastatin from Advicor, Niaspan alone, Mevacor alone, and coadministration of Niaspan and Mevacor.
CP-98-010419	Open-label, randomized, single-dose, 3-way crossover comparison of the bioavailability of niacin and lovastatin from Advicor under fasting conditions, after a low-fat snack, and after a high-fat snack.
97/04	Open-label, randomized, single-dose, 2-way crossover study to determine the bioequivalence of Niaspan 500 mg tablets manufactured at different facilities.
97/05	Open-label, randomized, single-dose, 2-way crossover study to determine the bioequivalence of Niaspan 1000 mg tablets manufactured at different facilities.
CP-98-010420	Open-label, randomized, single-dose, 2-way crossover study to determine the bioequivalence of Advicor 750 mg tablets relative to Niaspan 750 mg tablets manufactured at different facilities.

The above 6 studies have been reviewed in detail in the Biopharm review.

The four clinical safety and efficacy studies are as follows:

1) Two studies (MA-98-010414 and MA-98-010406) were randomized, double-blind active-comparator studies, comparing Advicor to its two individual active components Niaspan and lovastatin
2) One study was an open-label, uncontrolled, 52 week study of Advicor for safety and efficacy (MA-98-010407)
3) One study was an

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The safety and efficacy studies are summarized in the following table

Table 8: Advicor Safety and Efficacy Studies

Protocol Number	Study Design
MA-98-010414 (MA-14)	Double-blind, randomized, controlled, dose-response study comparing Niaspan vs Advicor (3 dosage groups) vs lovastatin
MA-98-010406 (MA-06)	Double-blind, randomized, controlled, dose-ranging study comparing Niaspan vs Advicor (2 dosage groups) vs lovastatin
MA-98-010407 (MA-07)	Open-label, long-term, single-arm, uncontrolled safety and efficacy study of Advicor.
[ ]	]

Study — did not involve the administration of Advicor, and was considered only as additional safety information for Niaspan. Study — was therefore not reviewed in detail. The other three safety and efficacy studies were reviewed in detail and form the basis of this NDA review. The MA-07 study had not been completed at the time of the original NDA submission, and the efficacy information submitted for MA-07 is an interim analysis of the efficacy data. The safety information for MA-07 was updated at 4 and 8 months.

The two safety extension studies were submitted with the 8-month safety update, and contained a 48-week safety and efficacy extension study of MA-07, and study MA-98-010409 (MA-09), a 48-week extension study of the two double-blind studies MA-14 and MA-06. The additional safety studies are summarized in the following table

Table 9: Advicor Additional Safety Studies/Update

Protocol Number	Study Design
MA-98-010407 (MA-07)	48-week extension to MA-07. Open-label, uncontrolled, single-arm study of 300 patients rolled-over from the initial 52-week study.
MA-98-010409 (MA-09)	48-week extension to MA-14 and MA-06. Open-label, uncontrolled single-arm study of 106 patients entered after completing the 2 double-blind studies.

2. Population Studied

The selection of patients for the MA-06, MA-14, and MA-07 studies was based on the proposed labeling and target population for Advicor. Advicor was studied in adult patients, 18 years of age or older, with hypercholesterolemia types IIa and IIb, who were eligible for cholesterol-lowering drug treatment per NCEP guidelines (see Table 1).

3. Submission Goals

The Sponsor's main goal for this NDA submission is that Advicor will be approved for first-line treatment of hyperlipidemia types IIa and IIb. The Sponsor intends to demonstrate that combined treatment with niacin extended-release (Niaspan) and lovastatin is:

1. Superior to lovastatin alone and Niaspan alone in the treatment of elevated LDL-C
2. Superior to lovastatin alone and Niaspan alone in the treatment of elevated TG and low HDL-C.
3. Safe for chronic administration based on adverse events, clinical examination, and laboratory assessments.

To gain approval for these indications, Advicor's safety and efficacy profile must demonstrate its advantage over single agent therapy as a first-line treatment for hypercholesterolemia.

Additionally, the Division will evaluate Advicor for approval as a convenient second-line agent for patients who may require combination treatment for other lipid derangements. In this setting, Advicor must demonstrate better HDL-raising and TG-lowering than lovastatin alone, and better LDL-lowering than Niaspan alone.

III. Review of NDA 21-249 and Supportive Data

A. Protocol MA-98-010414

(Protocol MA-98-010414 will be referred to as MA-14 from this point forward)

1. Study Design for MA-14

a) Study Design

Protocol MA-98-010414 (MA-14) "Evaluation of the Safety and Efficacy of Advicor (a combination tablet of niacin extended-release/lovastatin immediate-release): A Dose-Response Study" was a 20-week, double-blind, randomized, controlled, dose-escalation study conducted at 16 clinical sites nationally. The study evaluated the efficacy and safety of Advicor vs Niaspan vs lovastatin in 164 patients with Type IIa and IIb hyperlipidemia and LDL-C levels warranting treatment per NCEP II guidelines.

b) Study Objectives

The objective of the study was to evaluate the dose-response relationships and safety of a range of Advicor doses in patients with dyslipidemia, and to evaluate the efficacy of various fixed combination doses of Advicor compared to each of the individual components (niacin and lovastatin).

c) Eligibility Criteria

(1) Inclusion Criteria

1) Men and women 21 years of age or older
2) Patient was willing to participate and sign Informed Consent
3) Patient had primary hypercholesterolemia Frederickson Type IIa or IIb
4) Patient had not taken lipid-altering or other prohibited medications for at least 6 weeks prior to randomization, or 4 weeks prior to qualification visits, and for the duration of the study
5) Female patients must not have been pregnant or breast-feeding. Women of childbearing potential must have used an oral contraceptive, an IUD, or a double barrier method of contraception

(2) Exclusion Criteria

1) Patient had an allergy or hypersensitivity to niacin, lovastatin, or their derivatives
2) Patient had a previous history (within 12 months of screening) of substance abuse or dependency
3) Patient had untreated or unsuccessfully treated psychiatric disease
4) Patient had used an investigational study medication or participated in an investigational study within 30 days of screening
5) Patient had taken a prohibited medication within 4 weeks of obtaining qualification labs. Prohibited medications were:
   - 3-isotretinoin (Accutane)
   - cyclosporin (Sandimmune)
   - troglitazone (Rezulin)

- oral erythromycin and/or any other oral macrolide antibiotic
- oral itraconazole and/or any other oral azole-type antifungal agent
- any HMG-CoA reductase inhibitor [atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor), pravastatin (Pravachol), simvastatin (Zocor), cerivastatin (Baycol)]
- any fibric acid derivative [gemfibrozil (Lopid), fenofibrate (TriCor), clofibrate (Atromid-S)]
- bile acid sequestrants [cholestyramine (Questran, Questran Lite), colestipol (Colestid), etc.]
- any product containing over 30 mg of niacin

Concomitant medications known to have minor effects on serum lipid levels were permitted if the dose had been stable for 1 month prior to randomization and remained stable throughout study participation, e.g., thiazide diuretics, systemic beta-blockers, systemic corticosteroids, and psyllium products. Estrogen replacement and thyroid replacement therapy were allowed if the doses had been stable for at least three months prior to randomization and throughout the study. The Thyroid Stimulating Hormone (TSH) must have been within normal limits (WNL) for patients on thyroid replacement.

6) Patient had a history of:
   - Active gallbladder disease within one year (cholecystectomy was allowed)
   - Persistent treated or untreated severe hypertension
   - Unstable angina
   - Myocardial infarction, coronary artery surgery, angioplasty, or stroke within the preceding six months
   - Significant renal disease (serum creatinine $\geq$1.5 mg/dL)
   - Significant hepatic disease (AST or ALT >1.3 X ULN)
   - Congestive heart failure (NYHA class III or IV)
   - Active gout symptoms and/or uric acid levels >1.3 X ULN
   - Active peptic ulcer disease
   - Arterial bleeding
   - Type 1 diabetes or uncontrolled type 2 diabetes (HgA1C >8%)
   - Active cancer or a diagnosis of cancer within the last 5 years (excluding basal cell carcinoma)
7) Patient had any health condition or laboratory abnormality which, in the opinion of the Investigator, may have been adversely affected by the procedures or medications in this study
8) Patient had been treated with Lorelco (probucol) within 1 year prior to screening

d) Study Visits and Procedures

The study visits and procedures are summarized below and in the following table.

Table 10: MA-14 Study Visits and Procedures

	Qualification Visits	Treatment Visits					
Week	**-8 to -1**	**0**	**4**	**8**	**12**	**16**	**20/ET**
Procedure							
Sign Informed Consent	X						
Medical History	X						
Physical Exam		X					X
Vital Signs	X	X	X	X	X	X	X
ECG	X						
Dietary Instruction/Evaluation	X						
3-Day Diet Log Collected		X			X		X
Serum Chemistries	X		X	X	X	X	X
Fasting Lipid Panel	X		X	X	X	X	X
Hematology	X						X
Urinalysis	X						X
HgA1C(diabetics only)	X				X		X
PT/PTT	X						X
TSH (thyroid replacement only)	X						
Pregnancy Test (if applicable)	X						
Flushing Logs Dispensed		X	X	X	X	X	
Adverse Events Query			X	X	X	X	X
Dispense Study Medication		X	X	X	X	X	
Collect Study Medication			X	X	X	X	X

(1) Screening and Qualification Visits (Weeks –8 to –1)

All participants were recruited at 16 study sites, and screened for eligibility including medical history, ECG, laboratory assessment [including serum chemistry, hematology PT/PTT, HCG (females age <60), TSH (patients on thyroid replacement), HgA1C (type 2 diabetics), and urinalysis], and vital signs. All patients underwent diet assessment and teaching, and were required to follow an NCEP Step 1 diet for at least 4 weeks prior to obtaining qualification laboratories. A 3-day diet log was dispensed during qualification, and was to be completed prior to the randomization visit. Patients using lipid-lowering medications were required to discontinue their use for at least 4 weeks prior to obtaining qualification labs.

For qualification, 2 fasting lipid profiles within 7-10 days of each other were obtained. Lipid profiles could be repeated twice if needed for qualification, and the mean of 2 consecutive lipid profiles was used for qualification. In order to be randomized, patients must have met all of the following qualification criteria:

1) Low density lipoprotein cholesterol (LDL-C) based on NCEP II guidelines must have been:
   a) For patients with diabetes or a history of CHD: mean LDL $\geq$130 mg/dL
   b) For patients with 2 or more CAD risk factors: mean LDL $\geq$160 mg/dL
   c) For patients with fewer than 2 CAD risk factors: mean LDL $\geq$190 mg/dL
2) LDL lower value within 12% of the greater value, calculated as

$$\frac{[\text{LDL(higher)} - \text{LDL(lower)}]}{\text{LDL(higher)} \times 100}$$

3) Mean triglycerides $\leq$800 mg/dL
4) ALT and AST $\leq$1.3 X ULN

(2) Randomization Visit (Week 0)

Qualifying patients returned to the study center within 7-14 days of the last qualification visit. Three-day diet logs were returned and evaluated prior to randomization. Qualifying patients were randomized to one of 5 blinded treatment groups. Patients then underwent physical examination including medical history update and vital signs (blood pressure, pulse, height and weight), and randomization. Flushing logs and study medication were dispensed.

(3) Post-Randomization Visits (Weeks 4, 8, 12 and 16)

Patients underwent vital sign measurements and laboratory assessment [fasting lipid profile and serum chemistry]. Adverse events and concomitant medications were reviewed. Flushing logs and study medication were collected, and medication for the next 4 weeks was dispensed. At Week 12 only, a 3-day diet log was collected and HgA1C (diabetics only) laboratory testing was performed.

(4) End of Study (Week 20) or Early Termination

Patients underwent a physical exam including vital signs, and laboratory assessment [fasting lipid profile, serum chemistry, hematology, HgA1C (diabetics only), PT/PTT, and urinalysis]. Adverse events and concomitant medications were reviewed. Three-day diet logs and all study medication were collected.

e) Study Medication Dispensing and Compliance

Study patients were randomly assigned to one of five treatment groups as follows
Group A: Niaspan [mg]
Group B: Advicor/10 (Advi/10) [mg Niaspan/10 mg lovastatin]
Group C: Advicor/20 (Advi/20) [mg Niaspan/20 mg lovastatin]
Group D: Advicor/40 (Advi/40) [mg Niaspan/40 mg lovastatin]
Group E: lovastatin [mg]
Randomization occurred at the study sites using blocks of five dispensed sequentially by blinded study personnel.

All five study treatments were administered in a forced dose-escalation fashion at 4-week intervals for a total of 20 weeks. Study treatments were dosed once daily at bedtime with

a low fat snack. Patients took 4 tablets a day during Weeks 1-16, and 5 tablets a day during Weeks 17-20. The dose titration schedule by treatment group is as follows

Table 11: MA-14 Dose Titration Schedule

	Weeks				
Treatment	**1-4**	**5-8**	**9-12**	**13-16**	**17-20**
Niaspan (mg)	500	1000	1500	2000	2500
Advi/10 (mg/mg)	500/10	1000/10	1500/10	2000/10	2500/10
Advi/20 (mg/mg)	500/20	1000/20	1500/20	2000/20	2500/20
Advi/40 (mg/mg)	500/40	1000/40	1500/40	2000/40	2500/40
Lovastatin (mg)	10	10	20	20	40
Number of tablets	4	4	4	4	5

Study medications were visually identical, supplied in blister cards, and dispensed for a 4-week period + 7 days extra medication. Unused medication was collected at the following study visit, and compliance was determined by a tablet count.

The study medication tablet consisted of:
Niaspan - Niacin extended-release (ER) 500 mg
Advicor - Niacin ER 500 mg + lovastatin 10 mg
Lovastatin - placebo + lovastatin 10 mg
Placebo - placebo
Tablet content varied by visit and by treatment group. Tablets given by week by treatment group are as follows

Table 12: MA-14 Tablet Content

	Weeks				
Treatment	**1-4**	**5-8**	**9-12**	**13-15**	**17-20**
Niaspan dose (mg)	**500**	**1000**	**1500**	**2000**	**2500**
Niacin ER 500 mg tablets	1	2	3	4	5
Placebo tablets	3	2	1	0	0
Advi/10 dose (mg/mg)	**500/10**	**1000/10**	**1500/10**	**2000/10**	**2500/10**
Advicor 500/10 tablets	1	1	1	1	1
Niacin ER 500 mg tablets	0	1	2	3	4
Placebo tablets	3	2	1	0	0
Advi/20 dose (mg/mg)	**500/20**	**1000/20**	**1500/20**	**2000/20**	**2500/20**
Advicor 500/10 tablets	1	2	2	2	2
Lovastatin 10 mg tablets	1	0	0	0	0
Niacin ER 500 mg tablets	0	0	1	2	3
Placebo tablets	2	2	1	0	0
Advi/40 dose (mg/mg)	**500/40**	**1000/40**	**1500/40**	**2000/40**	**2500/40**
Advicor 500/10 tablets	1	2	3	4	4
Lovastatin 10 mg tablets	3	2	1	0	0
Niacin ER 500 mg tablets	0	0	0	0	1
Lovastatin dose (mg)	**10**	**10**	**20**	**20**	**40**
Lovastatin 10 mg tablets	1	1	2	2	4
Placebo tablets	3	3	2	2	1

f) Efficacy and Endpoint Measures

Primary: The primary efficacy analysis is the mean percent change from baseline in LDL-C for each dose compared among the Advicor, lovastatin, and Niaspan treatment groups.

Secondary: Secondary efficacy measures are mean percent change from baseline in:

1) Apoprotein B [Apo B]
2) Total cholesterol [TC]
3) High density lipoprotein cholesterol [HDL-C]
4) Triglycerides [TG]
5) Lipoprotein a [Lp(a)]
6) TC:HDL-C ratio
7) LDL-C:HDL-C ratio

Safety: Safety was assessed by measuring serum transaminases, chemistry and hematology profiles, urinalysis, physical examination including vital signs, and adverse events.

2. Results

Two hundred ninety-nine (299) patients were screened at 16 study sites. One hundred sixty-four (164) patients were randomized between 01-May-1999 and 23-Sep-1999. As all randomized patients in this study took at least one dose of study medication, the Intent-To-Treat (ITT) and randomized patient populations are the same. The patients were randomized into treatment groups as follows

Table 13: MA-14 Patients Randomized by Treatment Group

		Treatment				
	All	**Niaspan**	**Advi/10**	**Advi/20**	**Advi/40**	**Lovastatin**
Patients Randomized, n =	164	31	34	34	32	33

a) Baseline Demographics and Patient Characteristics

Overall, 52% of the randomized population was male and >80 % was Caucasian. Patient ages ranged from 28-78 years, with a mean age of 59.3 years. Demographic data were not provided for the non-randomized (screen failure) patients, but 79/135 (59%) were not eligible for randomization due to failure to qualify by lipid inclusion criteria. Baseline characteristics and demographics for the treatment groups are summarized as follows

Table 14: MA-14 Baseline Demographics

	Randomized	Treatment				
	All	Niaspan	Advi/10	Advi/20	Advi/40	Lovastatin
Number of Patients, n =	164	31	34	34	32	33
Demographic Measure						
Gender, n (%)						
Male	85 (52)	17(55)	17(50)	18(53)	15(47)	18(55)
Female	79 (48)	14(45)	17(50)	16(47)	17(53)	15(45)
Age, years						
Mean	59.3	58.2	59.0	61.2	60.1	57.7
Median	61	57.0	58.5	63.5	62.0	63.0
min, max	28, 78	35, 78	35, 74	38, 75	31, 78	28, 78
Age ≥ 65 years, n (%)	63 (38)	8 (26)	14 (41)	15 (44)	13 (41)	13 (39)
Ethnicity, n(%)						
Caucasian	135 (82)	25(80)	29(85)	25(74)	27(84)	29(88)
Black	22 (13)	3(10)	5(15)	7(21)	4(13)	3(9)
Hispanic	1 (<1)	1(3)	0	0	0	0
Asian	6 (4)	2(6)	0	2(6)	1(3)	1(3)
Other	0	0	0	0	0	0
Risk Factors (RF)						
Diabetes, n (%)	15 (9)	4 (13)	2 (6)	4 (12)	4 (13)	1 (3)
Current smoker, n (%)	27 (16)	1 (3)	10 (29)	7 (21)	5 (15)	4 (12)
≥2 CAD RF, n (%)	118 (72)	23 (74)	25 (74)	24 (71)	24 (75)	22 (67)
<2 CAD RF, n (%)	46 (28)	8 (26)	9 (26)	10 (29)	8 (25)	11 (33)
Mean BMI, kg/M^2	29.0	29.5	29.0	28.3	30.2	28.4
Baseline Lipid Value						
Mean LDL-C, mg/dL	-	201.6	199.5	191.4	204.9	195.6
Mean HDL-C, mg/dL	-	41.8	45.3	43.2	45.4	45.3
Median Triglycerides, mg/dL	-	174.0	153.8	156.8	190.5	162.0
Mean Lp(a), mg/dL	-	39.4	45.6	50.0	36.4	46.0

b) Patient Disposition

(1) Screening and Randomization

Of the 299 screened patients, 135 (45% of total screened) were not randomized. Of the 135 non-randomized patients, 79 (59% of screen failures) were not eligible for randomization due to failure to qualify by lipid inclusion criteria. Patients failing to meet eligibility criteria are summarized in the following table

Table 15: MA-14 Patients Failing to Meet Eligibility Criteria

Eligibility criteria not met, n = 135	n (%)
Failure to have appropriate lipid levels per inclusion criteria	79 (59)
Withdrawal of consent	23 (17)
Lost to Follow-up	14 (10)
Abnormal laboratory value	9 (7)
Other medical	7 (5)
Other non-medical	3 (2)